HUMAN TISSUE SAMPLES: NIH RESEARCH POLICIES AND PRACTICES

HEARINGS

BEFORE THE

SUBCOMMITTEE ON OVERSIGHT AND INVESTIGATIONS

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HUMAN TISSUE SAMPLES: NIH RESEARCH POLICIES AND PRACTICES

TUESDAY, JUNE 13, 2006

HOUSE OF REPRESENTATIVES,
COMMITTEE ON ENERGY AND COMMERCE,
SUBCOMMITTEE ON OVERSIGHT AND INVESTIGATIONS,
Washington, DC.

The subcommittee met, pursuant to notice, at 2:04 p.m., in Room 2123 of the Rayburn House Office Building, Hon. Ed Whitfield (Chairman) presiding.

Members present: Representatives Stearns, Walden, Burgess, Blackburn, Barton (ex officio), Stupak, Baldwin, and Whitfield.

Staff present: Mark Paoletta, Chief Counsel for Oversight and Investigations; Alan Slobodin, Deputy Chief Counsel for Oversight and Investigations; Mike Abraham, Legislative Clerk, Ryan Ambrose, Legislative Clerk; John Ford, Minority Counsel; Jessica McNiece, Minority Research Assistant; and William Garner, Minority Professional Staff Member.

MR. WHITFIELD. I would like to call this hearing to order this afternoon. Today and tomorrow, the subcommittee examines the important issue of human tissue samples. These samples, such as blood, cells, and spinal fluid are raw material of biomedical research that can help improve our healthcare. These samples matter because of their growing importance in biomedical research. Detailed genetic and other biological marker information can be derived from these samples and with such information, we can dramatically improve the way we diagnose and treat disease.

The National Institutes of Health is at the forefront in collecting these samples and using them for unique medical research not conducted in universities or industrial labs. NIH scientists obtain these samples through a great deal of care and work with patients and healthy volunteers who participate in biomedical experiments.

The ability of NIH researchers to obtain samples from people and the resources and the freedom to research relies on a basic trust. These hearings focus on whether that trust used to obtain human samples for research at NIH is working as well as it should.

We look at this important question through the prism of a case study. The study involves Dr. Trey Sunderland of the National Institute of Mental Health, and the vials of human spinal fluid and plasma he

shipped to Pfizer from 1998 to 2004. Some members of the subcommittee may recall Dr. Sunderland's name from the subcommittee's June 2004 hearing, where we revealed the discrepancies between information provided by Pfizer documenting over $500,000 in outside consulting payments to Dr. Sunderland over a 5-year period, and the information that was given to NIH and to the committee showing no documentation of disclosure or approval of these very same outside consulting activities for Dr. Sunderland. NIH has investigated these discrepancies and made its determination of multiple violations of legal and ethical requirements.

But today's inquiry is about an investigation beyond those compliance issues. We are concerned primarily about the integrity of NIH research. The committee's concerns in this area were prompted in part by Dr. Susan Molchan, who is the Program Director for Alzheimer's disease research at the National Institute of Aging. From 1993 to 1995, she conducted a small clinical trial involving the collection of spinal fluid from about 25 people, some patients with Alzheimer's disease and some normal volunteers, and used lithium as a probe for potential biomarkers of Alzheimer's disease in spinal fluid and blood. She had published two papers and told the committee staff that she had used, at the very most, 20 percent of the spinal fluid collected. The unused spinal fluid remains stored in freezers at NIMH geriatric/psychiatric branch. The chief of the geriatric/psychiatric branch, Dr. Trey Sutherland, assumed control of the spinal fluid and the samples after Dr. Molchan left.

In the fall of 2004, Dr. Molchan was at the NIA and was trying to assist an outside researcher in getting unused samples from Dr. Molchan's unfinished study. Ultimately by March of 2005, she learned that Dr. Sunderland was only able to produce a very small percent of the unused spinal fluid that remained from her lithium study, and that the clinical data from that study had been purged. She was concerned about what happened to the more than 95 percent of the unused spinal fluid samples left in the freezer and to the data.

She pursued her concerns for several weeks during 2005 through various NIH channels and with the Office of Inspector General, Department of Health and Human Services as well. In April 2005, she contacted staff with the Committee on Energy and Commerce. After more preliminary work from the committee staff, the bipartisan leadership of the committee and the subcommittee started a broad investigation on the issue of human tissue samples at the National Institutes of Health and the particular case involving Dr. Sunderland and the spinal fluid samples.

The committee has been investigating this issue for over a year now. We have requested records and information. After reviewing the records and interviewing people, the committee staff assembled evidence in its report for the subcommittee members. The report, which will be placed in the hearing record, raises some very troubling questions.

Dr. Sunderland is a leading researcher in the area of Alzheimer's disease. For years, he has been interested in finding a diagnostic test for this disease. Pfizer was also interested in this goal, and this joint interest was worthy of a scientific collaboration between government and the private sector. In 1998, Dr. Sunderland had an opportunity to pursue this project legitimately with Pfizer and a British biotechnology firm under existing laws and policies that promote this public/private partnership.

Instead, disappointingly, the evidence shows that Dr. Sunderland used his public office to provide spinal fluid and plasma samples to Pfizer at the same time that he engaged in personal consulting with Pfizer about these very same samples. He did not disclose these consulting arrangements to NIH; this subcommittee exposed them. And even after he was under investigation, the records show that Dr. Sunderland did not accurately describe the nature of his consulting activities with Pfizer. According to the records obtained by the committee, Dr. Sunderland provided over 3,000 spinal fluid and plasma samples to Pfizer and received $285,000 from Pfizer for two different projects using these samples.

Congress and NIH have provided the proper mechanisms for government/industry partnership and we encourage it. Federal laws and policies do not permit, however, NIH scientists to profit personally from their jobs and their patients by providing irreplaceable government assets. Unfortunately, the evidence before us shows Dr. Sunderland operated outside that system. Why did he choose to enrich himself? There were mechanisms available to get the resources for his lab as part of this collaboration, but there are not records that we have been able to find or information showing that this was done, and why not?

There were mechanisms available to him and NIH scientists to obtain patents and royalties. Dr. Sunderland, however, assigned his patent rights to Pfizer under one of the two research projects and he was listed as a co-inventor at his home address. Why didn't he tell NIH? Why didn't he protect the rights of NIH? And what about the Alzheimer's disease patients and human volunteers who had their spines punctured and then had to lie on their sides for three hours after each procedure? Did Dr. Sunderland tell them he was going to make money from their spinal fluid, and why did he make a statement and reaffirm to NIH investigators that his outside activities were with one part of Pfizer and that the material transfer agreement, his official activities in

providing the samples were with another part of Pfizer, when the same Pfizer official signed the consulting agreement and the material transfer agreement? Why did Dr. Sunderland, who has an excellent reputation as a researcher and is considered beyond reproach as the Chairman for 10 years of NIH's Institutional Review Board put himself in the position of being under investigation?

In learning more about the circumstances of Dr. Sunderland's conduct, the committee's investigation uncovered other serious questions about the adequacy of NIH policy and oversight regarding human tissue samples. For example, Dr. Sunderland transferred the human tissue samples taken from subjects for a new research purpose without consulting with NIH officials or even the Institutional Review Board in charge of protecting these samples. Is that a violation of ethical rules, or is that an acceptable practice?

From the available evidence, Dr. Sunderland alone, it appears, decided to transfer a large number of human tissue samples to Pfizer, a company in which he had a financial consulting interest. But would Alzheimer's disease research have been better served if Dr. Sunderland had consulted with the other NIH experts and tested the samples, not just with the technology involved in the Pfizer projects, but with other technologies with other companies as well?

We hope to gain more insight to these matters and improve the operations of NIH for the benefit of the American people. Already, this investigation has led NIH to revise informed consent requirements and has helped stimulate discussions within the Institutes to improve policies related to human tissue samples. Some of the concerns raised have also led to the Institutes making new inquiries about human subject protection and assignment of patent rights involved in the Dr. Sunderland matter.

Today, we will have one witness, and that is Dr. Susan Molchan, who helped raise these concerns over human tissue samples, and then tomorrow we will have witnesses from NIH, including the Deputy Director of Intramural Research, a former Pfizer scientist who worked with Dr. Sunderland, an associate of Dr. Sunderland's involved in the Pfizer activities.

I want to thank Chairman Barton for his support of this investigation, and Mr. Dingell and Mr. Stupak for their support, and we look forward to Dr. Molchan's testimony.

[The prepared statement of Hon. Ed Whitfield follows:]

THE PREPARED STATEMENT OF THE HON. ED WHITFIELD, CHAIRMAN, SUBCOMMITTEE ON OVERSIGHT AND INVESTIGATIONS

Today and tomorrow, the Subcommittee examines the increasingly important issue of human tissue samples. These samples – such as blood, cells, and spinal fluid – are the

raw material of biomedical research that can help improve our healthcare. These samples matter because of their growing importance in biomedical research. Detailed genetic and other biological marker information can be derived from these samples. With such information, we could dramatically improve the way we diagnose and treat disease.

The National Institutes of Health (NIH) is at the forefront in collecting these samples and using them for unique medical research not conducted in university or industry labs. NIH scientists obtain these samples through a great deal of care and work with patients and healthy volunteers who participate in biomedical experiments. The ability of NIH researchers to get samples from people and the resources and the freedom to research relies on trust. These hearings focus on whether that system of trust behind the human samples research at NIH is working as well as it could.

We look at this important question through the prism of a case study – an approach this Subcommittee uses often in its oversight hearings. The case study involves Dr. Trey Sunderland of the National Institute of Mental Health (NIMH) and the vials of human spinal fluid and plasma he shipped to Pfizer from 1998 to 2004. Some members of the Subcommittee may recall Dr. Sunderland's name from the Subcommittee's June 2004 hearing where we revealed the discrepancies between information provided by Pfizer documenting over $500,000 in outside consulting payments to Dr. Sunderland over a five-year period and the information given by NIH to the Committee showing no documentation of disclosure and approval of these very same outside consulting activities for Dr. Sunderland.

NIH has investigated these discrepancies and made its determination of multiple violations of legal and ethical requirements. But today's inquiry is about an investigation beyond these compliance issues. We are concerned about the integrity of NIH research.

The Committee's concerns in this area were prompted in part by Dr. Susan Molchan, Program Director for Alzheimer's Disease Research at the National Institute of Aging (NIA). From 1993 to 1995, she conducted a small clinical trial involving the collection of spinal fluid from about 25 people (some patients with Alzheimer's disease and some normal volunteers) and the use of lithium as a probe for potential biomarkers of Alzheimer's disease in spinal fluid and blood. In early 1997, Dr. Molchan left the NIMH, but she had not finished this study. She had published two papers and told the Committee staff that she had used at the very most 20% of the spinal fluid collected. The unused spinal fluid remained stored in freezers at the NIMH Geriatric Psychiatry Branch. The Chief of the Geriatric Psychiatry Branch, Dr. Trey Sunderland, assumed control of the spinal fluid samples after Dr. Molchan left NIMH.

In the fall of 2004 Dr. Molchan was at the NIA and was trying to assist an outside researcher in getting unused samples from Dr. Molchan's unfinished study held at NIMH. Ultimately by March 2005, Dr. Molchan learned that Dr. Sunderland was only able to produce a small percent of unused spinal fluid that remained from the lithium study and that the clinical data from that study had been purged. (SLIDE 4) She was concerned about what happened to the more than 95% of the unused spinal fluid samples left in the freezer and to the data.

She pursued her concerns for several weeks during March-April 2005 through various NIH channels and with the Office of Inspector General (OIG), Department of Health and Human Services (HHS). In April 2005 she contacted staff with the Committee on Energy and Commerce. After more preliminary work from the Committee staff, the bipartisan leadership of the Committee and the Subcommittee started a broad investigation on the issue of human tissue samples at NIH and the particular case study involving Dr. Sunderland and the spinal fluid samples.

The Committee has been investigating this matter for a year. We requested records and information. After reviewing the records and interviewing people, the Committee staff assembled evidence in its report for the Subcommittee members. The report – which will be placed in the hearing record -- raises some troubling questions.

Dr. Sunderland is a leading researcher in the area of Alzheimer's disease. For years, he had been interested in finding a diagnostic test for this disease. Pfizer was also interested in this goal. This joint interest was worthy of a scientific collaboration between government and the private sector.

In 1998 Dr. Sunderland had an opportunity to pursue this project legitimately with Pfizer and a British biotechnology firm under existing laws and policies that promote public-private partnerships. Instead, the evidence shows that Dr. Sunderland used his public office to provide spinal fluid and plasma samples to Pfizer. At the same time, Dr. Sunderland engaged in personal consulting with Pfizer about these very same samples. He did not disclose these consulting arrangements to NIH – this Subcommittee exposed them. Ever after he was under investigation, the records show that Dr. Sunderland did not accurately describe the nature of his Pfizer consulting activities to NIH. According to the records obtained by the Committee, Dr. Sunderland provided over 3,000 spinal fluid and plasma samples to Pfizer (SLIDE 5) and received $285,000 from Pfizer for two different projects using these samples. (SLIDES 1 and 2)

The Congress and NIH have provided the proper mechanisms for government-industry partnerships. Federal laws and policies do not permit NIH scientists to profit personally from their jobs and their patients by providing irreplaceable government assets. Unfortunately, the evidence before us shows Dr. Sunderland operated outside that system. Why did he choose to enrich himself? There were mechanisms available to get resources for his lab as part of this collaboration. But there are no records or information showing this was done. Why not?

There were mechanisms available to him and NIH scientists to get patents and royalties. Dr. Sunderland, however, assigned his patent rights to Pfizer under one of the two research projects and he was listed as a co-inventor at his home address. Why didn't he tell NIH? Why didn't he protect the rights of NIH? What about the Alzheimer's disease patients and human volunteers who had their spines punctured and then had to lie on their sides for three hours afterward? Did Dr. Sunderland tell them he was going to make money from their spinal fluid? Why did Dr. Sunderland make a statement and reaffirm to NIH investigators that his outside activities were with one part of Pfizer, and that the material transfer agreement, his official activities in providing the samples, were with another part of Pfizer when the same Pfizer official signed Dr. Sunderland's consulting agreements and the material transfer agreement? Why did Dr. Sunderland – who had an excellent reputation as a researcher and was considered beyond reproach as the Chairman for 10 years of NIMH's Institutional Review Board – put himself in the position of being under investigation?

In learning more about the circumstances of Dr. Sunderland's conduct, the Committee's investigation uncovered other serious questions about the adequacy of NIH policy and oversight regarding human tissue samples. For example, Dr. Sunderland transferred the human tissue samples taken from human subjects for a new research purpose without any consultation with NIH officials or the Institutional Review Board in charge of protecting human subjects. Is that a violation of ethical rules or acceptable practice? From the available evidence, Dr. Sunderland alone decided to transfer a large number of human tissue samples to Pfizer, a company in which he had a financial consulting interest. But would Alzheimer's disease research have been better served if Dr. Sunderland had consulted with other NIH experts and tested the samples not just with the technology involved in the Pfizer projects but with other technologies with other companies?

We aim at these hearings to gain more insight into these matters and improve the operations of NIH for the benefit of the American people. Already this investigation has led NIH to revise informed consent requirements and has helped stimulate discussions within NIH to improve policies related to human tissue samples. Some of the concerns

raised have also led to NIH making new inquiries about human subject protection and assignment of patent rights involved in the Dr. Sunderland matter.

Today we will hear from Dr. Susan Molchan who helped raise the concerns over human tissue samples. Tomorrow, we will have witnesses from NIH including the Deputy Director for Intramural Research, a former Pfizer scientist who worked with Dr. Sunderland, an associate of Dr. Sunderland involved in the Pfizer activities, and Dr. Sunderland himself.

I want to thank Chairman Barton for his support of this investigation. I also want to thank Mr. Dingell and Mr. Stupak for their support of this investigation. I also want to note that Pfizer was cooperative with the Committee's investigation and we appreciate that.

I look forward to hearing from the witnesses.

MR. WHITFIELD. At this time, I recognize Mr. Stupak.

MR. STUPAK. Thank you, Mr. Chairman, and thanks for holding this hearing today. We are going to have another one tomorrow.

This inquiry has been a bipartisan effort for the past year. The staff report released today provides the committee with a sound basis to do our work. I compliment the bipartisan committee staff work and their report. Through no fault of our staff, I do note that this investigation took much longer than should have been necessary. The National Institutes of Health and/or its overseers at the Department of Health and Human Services apparently had a hard time understanding our bipartisan request letter. Like other initial inquiries from the committee, they originally treated our request like a nuisance, something to respond to in a perfunctory way.

For instance, instead of supplying the committee with documents showing the disposition of the specific spinal fluid samples as requested, NIH gave us unsatisfactory excuses, such as possible freezer failure. We subsequently learned that NIH had records of the samples we requested, which were among 3,300 tubes of fluid samples shipped to Pfizer.

In the 2004 conflicts of interest investigation, the subcommittee discovered that about 100 NIH scientists failed to report income from the 20 drug companies that the committee had surveyed. Pfizer and other drug companies had the records; of course, NIH did not. Fortunately for this investigation, when we could not get the records of samples shipped out of the National Institute of Mental Health lab, Pfizer again had the records. I find it very disturbing that Pfizer has kept better records than NIH.

Interestingly, both of these investigations touched on a specific National Institute of Mental Health lab chief, Dr. Trey Sunderland. Only after this subcommittee provided this information to NIH 2 years ago did NIH become aware of Dr. Sunderland's receiving over $500,000 from Pfizer without reporting it. Yet, when we requested an accounting of the human tissue samples in Dr. Sunderland's control, NIH officials apparently accepted his explanation that such records did not exist. This

represents a complete lack of due diligence and negligence on the part of NIH. Unfortunately, the performance of the Department of Health and Human Services Inspector General, was similarly lacking. Because there is an ongoing inquiry, we will delay the examination of the performance of those investigators, but our preliminary information is that this IG continues to ignore its first responsibility, which is to keep the Department clean.

Mr. Chairman, the NIH has much to account for today. Priceless human tissues samples, samples from a unique collection that is not likely to be replicated, even at NIH, were shipped without any authority, any oversight, any accountability for a private research effort that was evaluated by a single government employee. That employee was Dr. Sunderland, a lab chief who, in the end, would pocket $285,000 from his decisions. We estimate that those samples cost NIH over $6 million, and took 15 years to collect.

As you noted, Mr. Chairman, spinal fluid is not easy to obtain. It involves three or more hours of inconvenience and often considerable pain for each volunteer on each occasion. People volunteered those samples to advance Alzheimer's research, most often because they or their loved ones suffered from this disease. The volunteers trusted the judgment that NIH would put their samples to best use. Unfortunately, NIH's failure to supervise its employees permitted a single scientist to make the judgment to give away irreplaceable samples. The lack of oversight also allowed Dr. Sunderland to take some 140 days of travel to perform his Pfizer consults. The failure to demand accountability allowed one of the two corroborative research projects to proceed without any protection of NIH's right to the resulting data or right to intellectual property resulting from the research. As a result, Pfizer owns all research products.

Of course, NIH didn't know any of this until we asked, because they have no uniform audit policy for acquisition, use, and/or storage of human tissue samples; storage and protection of data generated by their research; determination of whether human subject protection and informed consent are assured after any specific protocol is ended; accounting for leave of senior employees; assuring that the appropriate legal instruments are used when human tissues are transferred; or accounting for the fruits of corroborative research data and patents.

Mr. Chairman, it is time to rectify the inadequate oversight that has enabled these reckless activities to occur. Congress entrusts NIH with billions of dollars each year. Biomedical research needs to be guided by an unbiased assessment of producing strategies for diagnosis or treatment, not whether an NIH researcher maximizes his or her personal gain. Furthermore, thousands of Americans entrust NIH with their

personal medical histories, tissue samples, and other information each year to help find cures for diseases. We need to honor their commitment by ensuring that the highest scientific standards are upheld.

Mr. Chairman, I yield back the balance of my time.

MR. WHITFIELD. Thank you, Mr. Stupak.

At this time, I will recognize the gentleman from Texas, Dr. Burgess.

MR. STUPAK. Mr. Chairman, if I may, before Dr. Burgess, I ask unanimous consent to enter into the record the statement of Mr. Dingell, the Ranking Member of this committee. Thank you.

[The prepared statement of Hon. John D. Dingell follows:]

THE PREPARED STATEMENT OF THE HON. JOHN D. DINGELL, A REPRESENTATIVE IN CONGRESS FROM THE STATE OF MICHIGAN

Mr. Chairman, thank you for holding this hearing and initiating this bipartisan investigation. This inquiry is an example of how productive oversight can be when it is truly bipartisan. And it has been bipartisan from the first Chairman's letter to the staff report we have before us today. You and Representative Stupak have worked together and our staffs have worked together each step of the way.

What have we uncovered? For one thing a number of serious deficiencies in individual National Institutes of Health (NIH) processes that are enumerated in the staff report. No one looks to see if priceless human tissue samples are being put to their best use. No one is looking to see if human subject protection rules are followed. No one has to account for his or her time or budget.

Trusting scientific decisions to the scientists is one thing. Giving carte blanche to individual researchers to spend funds and divert precious human tissue resources derived from patients under their care is quite another.

Congress has taken the approach that biomedical research decisions are best left to the scientists. This is as it should be. We owe it to the taxpayers, however, to ensure that the scientists who make decisions regarding very expensive life and death research options do so in a rational manner with accountability at least within the scientific community.

These investigations and the conflict of interest hearings held in 2004 have exposed a severe structural weakness in the oversight functions within NIH. First it was ethics, now it is something even broader. Dr. Zerhouni did a good job tightening up the ethical environment after our last set of hearings. I hope Dr. Gottesman will undertake a similar clean-up campaign designed to return accountability to this great institution.

MR. BURGESS. Thank you, Mr. Chairman, and thank you for your continued leadership in the investigation that has become another very important public health issue.

During my tenure in Congress, I have had the privilege of visiting the National Institutes of Health several times. After each visit, I come away encouraged; encouraged by the research and the studies that the scientists perform on a daily basis. After each visit, my hope that a cure for cancer, a cure for Alzheimer's will be found, if not during my lifetime, then perhaps during the lifetime of my children.

I would like to take this opportunity to sincerely thank the doctors, researchers, and scientists at the National Institutes of Health for their dedication to such a noble profession. It is my opinion that outside consulting by scientists is not within itself an unethical practice. While outside consulting is currently prohibited by NIH employees, I believe that these types of arrangements can be beneficial to society as a whole if constructed in an ethical and transparent manner.

The situation before us involving Dr. Sunderland is an egregious example of how the system can fail if there is lack of transparency and a lack of ethical behavior. Dr. Molchan, thank you for bringing this situation to our attention.

In preparation for today's hearing, the committee released a bipartisan staff report to the members of this subcommittee. I think it is important to note that the bipartisan staff report came to a concluding paragraph, and I am quoting here, "It should be noted that the committee staff found no evidence that Pfizer had any knowledge relating to the questionable conduct of Dr. Sunderland in connection with the April, 1998, material transfer agreement and subsequent shipments of samples." The unethical practice lies clearly and solely with Dr. Sunderland.

Congress continues our work on reauthorization of the National Institutes of Health, a program that spends almost $30 billion a year, and it is money well spent. I feel certain that we can use the lessons learned today and tomorrow throughout the reauthorization process. It is our role to provide adequate oversight over the National Institutes of Health and ensure that taxpayer dollars and other resources, including tissue samples, are used in a worthwhile and ethical manner. We must not abrogate our responsibility to the American public regarding this important task.

Mr. Chairman, again I thank you for holding this hearing, and look forward to a lively discussion on the procedures concerning human tissue samples. I will yield back the balance of my time.

MR. WHITFIELD. Thank you, Dr. Burgess, and I would, without objection, want to enter into the record the staff report on this entire issue, as well as those slides and the exhibits. Without objection, so ordered.

[The information follows:]

A STAFF REPORT

For the Use of the Subcommittee on Oversight and Investigations
In Preparation for Its Hearing,

"Human Tissue Samples: NIH Research Policies and Practices," June 13-14, 2006

This staff report was written by the Majority and Minority Committee staff of the House Committee on Energy and Commerce.

Background

Human tissues are biological materials defined as "including everything from subcellular structures like DNA, to cells, tissue (bone, muscle, connective tissue, and skin), organs (e.g., liver, bladder, heart, kidney), blood, gametes (sperm and ova), embryos, fetal tissue, and waste (urine, feces, sweat, hair and nail clippings, shed epithelial cells, placenta)."[1] For purposes of the Subcommittee's inquiry, this report focuses on biological materials most frequently used in biomedical research such as tissues and cells. These are raw biological materials extracted from human beings that are to be distinguished from the biological inventions derived from such samples. These extracted tissues are stored and generate portions of tissues called samples.

Ever since 1858 when Rudolf Virchow wrote his famous book that detailed how changes in cells accounted for diseases in organs, human tissue samples have been the foundation of biomedical research.[2] In its 1999 report, the RAND Corporation published a "conservative estimate" that more than 307 million tissue samples from more than 178 million people were stored in the United States.[3] This number was reportedly increasing by more than 20 million samples a year. [4] Tissue samples have played a central role in major studies such as the Framingham studies on heart disease and the Women's Health Initiative (WHI), one of the largest women's health studies in which over a 15-year period, 161,000 women gave blood, urine, and other samples to investigators.[5] Human tissue samples also have significant value to biotechnology and pharmaceutical companies because these materials "can help them: reduce drug development times; develop new therapies and drugs; react quickly to unexpected adverse reactions; and identify new assay techniques or biomarkers."[6]

The issue of human tissue samples has assumed greater importance at the National Institutes of Health (NIH) and strengthened the need for more guidance to NIH-funded institutions (NIH's extramural research program that are more than 80 percent of the NIH's budget) as well as for the Institutes and Centers at the NIH that conduct their own research (NIH's intramural research program). As noted by the NIH's Director of the Office of Science Policy to NIH staff: "[H]uman specimen repositories and the use of human specimens and data are becoming an increasingly important part of our efforts to

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[1] Eiseman, E. and Castillo, J., Handbook of Human Tissue Sources, RAND Monograph Report, 7 (1999). See also U.S. Congress, Office of Technology Assessment, New Developments in Biotechnology: Ownership of Human Tissues and Cells – Special Report, OTA-BA-337 (March 1987) at 3.

[2] Hakimian, R. and Korn, D., "Ownership and Use of Tissue Specimens for Research," Journal of the American Medical Association, November 24, 2004, at 2500.

[3] Eiseman, E. and Castillo, J., Handbook of Human Tissue Sources, RAND Monograph Report,xvii (1999).

[4] Id. The National Bioethics Advisory Commission (NBAC) estimated that as of 1998, more than 282 million specimens of human biological materials were stored in the United States, accumulating at a rate of more than 20 million cases per year.

[5] Hindin, T., "Technology and Clinical Trials," Applied Clinical Trials, April 2006 at 12.

[6] Mills, J.F., "Precedents for Good Storage Practice," Applied Clinical Trials, April 2006 at 58.

advance basic science research and translate discoveries into improved medical care. However, the lack of consistency in the regulations, policies and procedures governing this type of research is creating confusion and barriers for researchers, repository managers, IRB [Institutional Review Board] staff, and their institutions. The magnitude of these challenges will likely grow as advances in informatics make it possible to make human datasets of unprecedented size and scope widely available to the research community."[7] In response to these perceived challenges and as part of the NIH Roadmap, the NIH is coordinating "a high priority effort to develop trans-NIH policies to govern NIH funded research with human specimens and data and to work across government to promote more consistent policies in this area."[8]

The focus of the inquiry for this hearing is the collection, storage, tracking, and use of human tissue samples in the NIH intramural research program.

The Committee's investigation in this area was prompted in part by concerns raised by Susan Molchan, M.D., Program Director for Alzheimer's Disease Research at the National Institute of Aging (NIA), to Committee staff in April 2005. Dr. Molchan had been a clinical researcher interested in Alzheimer's disease research at the National Institute of Mental Health (NIMH). From 1993 to 1995, she conducted a small clinical trial involving the collection of spinal fluid from about 25 people (some patients with Alzheimer's disease and some normal volunteers) and the use of lithium as a probe for potential biomarkers of Alzheimer's disease in spinal fluid and blood. In early 1997, Dr. Molchan left the NIMH, but she had not finished this study. She had published two papers and used at the very most 20 percent of the spinal fluid collected. The unused spinal fluid remained stored in freezers at the NIMH Geriatric Psychiatry Branch. The Chief of the Geriatric Psychiatry Branch was Trey Sunderland, M.D., who assumed control of the spinal fluid samples after Dr. Molchan left NIMH.

At a hearing on June 22, 2004, the Subcommittee on Oversight and Investigations revealed that Dr. Sunderland had received over $500,000 in payments from Pfizer during 1999-2004 for outside consulting and speaking without any record of prior approval for these activities or disclosure in his government financial-report filings.

By the fall of 2004, Dr. Molchan had been back at the NIH for three years, this time at the National Institute of Aging. At a meeting of top scientists and researchers, she learned that an outside researcher was pursuing funding for a lithium study similar to the one that Dr. Molchan had been unable to complete at NIMH. Spinal fluid samples are extremely valuable and very difficult to obtain. The outside researcher was very interested in getting Dr. Molchan's assistance in obtaining the spinal fluid samples and the linked clinical data from her study. Dr. Molchan agreed to assist. In the fall of 2004, Dr. Molchan asked Dr. Sunderland about the samples. After two months of inquiries, Dr. Sunderland sent two 0.5 cc samples from 10 subjects (about 2-3 percent of the unused amount of spinal fluid) to the outside researcher. In March 2005, Dr. Molchan asked Dr. Sunderland about the linked clinical data. Dr. Sunderland told her that that the data had been purged because it was over 5-7 years old and subject to purging.

Dr. Molchan was concerned about what happened to the more than 95 percent of the unused spinal fluid samples left in the freezer and to the data. In particular, after the public reports about Dr. Sunderland's undisclosed activities with Pfizer, she was concerned that Dr. Sunderland might have inappropriately or improperly diverted spinal fluid samples from her lithium study to Pfizer as part of his financial relationship. She pursued her concerns for several weeks during March-April 2005 through various NIH channels and with the Office of Inspector General (OIG), Department of Health and

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[7] Email on "Harmonization and Repositories," from Lana R. Skirboll, Ph.D., Director, Office of Science Policy, NIH, October 27, 2005 to various NIH staff.
[8] Id.

Human Services (HHS). In April 2005 she contacted staff with the Committee on Energy and Commerce.

In investigating her concerns and in general about the relevant NIH policies, the Committee staff learned from NIH officials that NIH had no uniform, centralized, and mandatory authority regulating the handling of human tissue samples. Some NIH laboratories kept a written record on the maintenance of these samples, but other NIH laboratories did not. Although there were explicit regulations defined in 42 C.F.R. 72.6 detailing the handling for hazardous biological materials and select agents, there was no explicit policy for the handling and accounting of human tissue samples. In addition, there was no formal inventory control or tracking system at NIH. If a freezer or other storage facility malfunctions and the human tissue samples become unusable, NIH laboratories were not required to account for the disposition of these samples. There was reason to believe that there were cases where NIH lost human tissue samples but had no record of what had been lost. Moreover, the lack of accountability left NIH wholly vulnerable to theft and diversion of valuable human tissue samples. These preliminary inquiries raised serious concerns over what was described to Committee staff by NIH officials as a fairly loose, ad-hoc approach to controlling human tissue samples.

On June 20, 2005, the bipartisan leadership of the full Committee and the Subcommittee sent a letter to the Director of the NIH requesting records and information on how human tissue samples are obtained, stored, tracked, and used in intramural programs throughout the institutes and centers of the NIH.[9] In the context of this investigation, the Committee focused primarily on spinal fluid samples and blood samples obtained from patients and other people participating in NIH intramural clinical trials.

One subject area of the Committee's June 20, 2005, request concerned the disposition of spinal fluid samples from patients with Alzheimer's disease and control subjects collected by scientists at the National Institute of Mental Health (NIMH) to be used in studies involving lithium. After the NIH's August 15, 2005, production, the Committee staff alerted the NIH that it appeared that not all responsive documents concerning these samples and Dr. Molchan's lithium study had been provided to the Committee. After the Committee staff raised these concerns with NIH about the production, the Committee did receive additional responsive records: three sets of records over the last few months from the NIH related to the spinal fluid samples and the lithium study, with the last set received on January 4, 2006. The Committee was troubled that the NIH did not produce all the responsive records in the first production, and produced these records only after Committee staff pressed several times for these additional responsive records. Most importantly, an NIH document received by the Committee in early 2006

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[9] The current total number of tissue samples at the NIH is unknown. As the NIH wrote to the Committee in a letter dated August 15, 2005:

"NIH does not maintain a central listing of all tissue samples in its possession. Each laboratory is responsible for storing and tracking all samples within its possession. NIH requires that each investigator obtaining such samples complete a Human Pathogen Registration Document, [ ], which requires information on the principal investigator, the location of the work, the agent or human blood, body fluid or tissue being worked with, and the names of all individuals working with the particular material being registered. The document does not require the investigator to supply the number of samples that he/she plans to work with or obtain. NIH currently has 390 Human Pathogen Registration Documents on file for human blood, body fluids, and/or tissues. Currently, 663 laboratories maintain human blood, body fluids, and/or tissue samples. [footnote omitted]. A total of 2340 employees are registered for work involving human blood, body fluids, and/or tissues. It is important to note that these numbers apply only to active research protocols.

In addition, NIH maintains biorepositories to provide investigators with pathological samples for research uses. Two are maintained by the National Cancer Institute, . . . "

documented that the Geriatric Psychiatry Branch (GPB) had sent spinal fluid samples to Pfizer from 538 subjects, who had participated in 14 different studies at NIMH. (See Exhibit 26) The protocol numbers listed on the documents showed that spinal fluid had been sent to Pfizer from subjects who had participated in Dr. Molchan's lithium study. That fact had not been previously disclosed to either Dr. Molchan or to the Committee.

On January 24, 2006, the bipartisan leadership of the Committee and the Subcommittee sent a letter to NIH requesting additional records about the disposition of the spinal fluid samples, the nature of NIMH oversight over human samples, and the way NIH/NIMH handled the Committee's request for records relating to the lithium study. In addition, on January 24, 2006, the bipartisan leadership of the Committee and the Subcommittee sent a letter to Pfizer, requesting records that could help determine the relationship, if any, between the disposition of the spinal fluid samples in question and Dr. Sunderland's official and/or private consulting activities with Pfizer.

Methodology

To review these issues related to human tissue samples, the Committee staff conducted extensive interviews with officials from NIH, former officials with NIH, officials with Pfizer, former officials with Pfizer, and other individuals.[10] Staff reviewed documents obtained by the Committee from NIH and Pfizer. Staff also reviewed public information and records.

NIH's Internal Investigation

The NIH's Office of Management Assessment (OMA) conducted an internal investigation of Dr. Sunderland's outside activity discrepancies first revealed in substantial part at the Subcommittee's June 22, 2004, hearing. The OMA found that Dr. Sunderland engaged in serious misconduct, in violation of HHS ethics rules and Federal law and regulation. The OMA confirmed that there was no documentation for Dr. Sunderland seeking prior approval or reporting the Pfizer activities. After the revelations of the Pfizer activities, Dr. Sunderland self-reported additional activities with other drug or biotech companies that lacked required documentation in which his payments almost totaled $200,000. Dr. Sunderland claimed that these were paperwork violations and that his outside activities did not constitute conflicts of interest with his official duties. In particular, Dr. Sunderland contended that his outside consulting did not relate to his official duty collaboration with Pfizer, which involved the sharing of spinal fluid samples under an April 1998 Material Transfer Agreement (MTA). However, the Ethics Review Panel convened by NIH in April 2005 found a direct overlap between the subject matter of Dr. Sunderland's official area of research and the scientific subject matter of his Pfizer consultancies. In addition, the Panel expressed concern over the 1998 MTA that Dr. Sunderland entered into with Pfizer while he maintained an ongoing consulting relationship with the company in the same area. In addition, in a memorandum dated October 12, 2005, the NIH Ethics Panel found that Dr. Sunderland's official duties constituted an overlap with some of unapproved outside activities with other drug companies he self-reported. (Exhibit 35)

On September 24, 2004, NIH referred an allegation to the Office of Inspector General - HHS (OIG) that Dr. Sunderland may have conducted outside activities during Government work hours without charging leave. Other records in connection with Dr. Sunderland beyond the issue in the referral have also been forwarded by NIH to the OIG.

[10] Committee staff requested numerous times to interview Dr. Sunderland, but through his attorneys he declined to be interviewed.

Committee's Investigation

It should be noted that the NIH investigated Dr. Sunderland's failure to obtain prior approval and disclose outside activities. NIH did not investigate the details of the underlying outside activities at issue. The concerns raised about human tissue samples led the Committee to investigate issues that arose from Dr. Sunderland's transfers of human tissue samples to Pfizer and examined the details of Dr. Sunderland's two principal consulting arrangements with Pfizer. This staff report is a preliminary report to assist the Members of the Subcommittee on Oversight and Investigations in preparing for the hearings to be held on June 13 and 14, 2006.

Question One: Did Dr. Sunderland obtain personal financial benefits from outside activities (with no record of disclosure to NIH or approval by NIH) with Pfizer, Inc., in any way because of actions he took in his official capacity in facilitating the transfer to Pfizer of human spinal-fluid samples and plasma samples, which were the assets and property of NIH?

Finding/Supporting Evidence: Yes. Records and interviews provide reasonable grounds to believe that Dr. Sunderland personally received $285,000 in compensation from Pfizer for activities that were derived directly from his official acts in providing Pfizer access to spinal fluid samples and plasma samples (over 3000 tubes of NIH property and linked clinical data) and that Dr. Sunderland used NIH employees and resources to provide such access.

Discussion:

The Committee's inquiry focused on the consulting agreements involving Dr. Sunderland's collaborations with Pfizer using human tissue samples procured from his Geriatric Psychiatry Branch in the National Institute of Mental Health (NIMH). Records from Pfizer show that the transfer of spinal fluid samples from Dr. Sunderland's branch at NIMH to Pfizer under an April 1998 Material Transfer Agreement coincided with the initiation of a two-year consulting agreement related to Dr. Sunderland's advice on information generated from those samples. The MTA and the consulting agreement were part of the same scientific collaboration. This consulting agreement and a spin-off consulting agreement from the collaboration netted Dr. Sunderland a minimum of $25,000 per year plus $2,500 per day for each one-day meeting (1998-2003). According to Pfizer, payments under these two contracts totaled $285,000, exclusive of reimbursement of travel expenses.[11]

Dr. Sunderland had been collecting human tissue samples and the related clinical information from NIH Alzheimer's disease patients and their families and controls since the early 1980s. This longitudinal collection of spinal fluid and blood samples was unique. While it was possible to purchase spinal fluid samples from Alzheimer's disease patients, individuals interviewed by Committee confirmed it was unlikely that anywhere but at the clinics of NIH could this unique historical collection of human tissue samples be assembled. Dr. Sunderland collected not only human tissue samples from Alzheimer's

[11] The consulting payments were in addition to sums Pfizer paid Sunderland for speeches or discussions with potential prescribers of Aricept and the occasional advisory board participation. Those payments added an additional $311,000 over roughly the same period of time as the consulting agreements. While such payments are now not permitted under the ethics rules, a special NIH ethics panel concluded that had Dr. Sunderland requested approval for these speeches, they would have been approved under the standards that predated the Committee's investigation and resulting reforms.

disease patients but also samples from their blood relatives as well as samples from controls.

The longitudinal aspect included in this collection gave the samples their unique character. At least some of the subjects had samples drawn both before and after the onset of Alzheimer's disease. Interviews and records obtained from Pfizer provide reasonable grounds to believe that obtaining these spinal fluid samples together with their clinical histories was a primary reason for Pfizer's interest in collaborating with Dr. Sunderland.

The samples themselves and the linked clinical data associated with these samples are generally considered to be valuable assets because such samples can be used for diagnostic, therapeutic, research, and commercial purposes. NIH has told the Committee that it takes the position that tissue samples are the property of the U.S. Government to the extent that NIH asserts an exclusive right to control the disposition and distribution of that material.[12] That would seem to be the case where the NIH has exclusive possession and control of the samples through its storage of these materials in its freezers in its own buildings, all funded by U.S. taxpayers. NIH continually asserts its ownership interests in such samples through its technology transfer policies and legal contracts such as Material Transfer Agreements (MTAs) and Cooperative Research and Development Agreements (CRADAs). In addition, the NIH-1884 form "Request for shipment" used to ship tissue samples to Pfizer noted that they were shipments of government-owned property. (See Exhibit 22)

Three legal documents were involved in the transfer of invaluable human tissue samples and the collaborative research that resulted: a material transfer agreement (MTA) between NIH and Pfizer signed by Dr. Trey Sunderland and two consulting contracts between Pfizer and Dr. Sunderland.

A material transfer agreement is to be distinguished from a collaborative research and development agreement (CRADA) and a consulting agreement involving the scientist and a company independent of the NIH. In a scientific endeavor such as the Pfizer/Sunderland collaboration, according to some NIH officials interviewed by Committee staff, a CRADA would have been the appropriate legal umbrella for this kind of research. (This is discussed in more detail later in this report.) Not only would that arrangement spell out the contributions and obligations of both parties, but it also would spell out the distribution of data and intellectual property rights between the government and the private sector firm, in this case Pfizer. Had a CRADA been negotiated, Dr. Sunderland would not have been able to receive any outside income for his efforts in the collaboration as it would have been part of his official duties.

Although NIH policies on technology transfer mechanisms were evolving and unclear in 1998, according to an NIH official interviewed by Committee staff, because the transfer involved a commercial entity, it is unlikely Pfizer could have taken possession of the samples of this value without a document authorizing the transfer. Absent a CRADA, an MTA was the instrument that specified the terms under which the NIH would release human tissue samples for a specific research purpose. The MTA did not obligate Pfizer to share the resulting data with NIH nor did it specify that the government retained any intellectual property right to the fruits of the proposed research.

Based on its past investigations of NIH scientists' outside consulting agreements, Committee staff believes that Pfizer would not have entered into a scientific collaboration

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[12] In an attached response to an e-mail dated May 12, 2006, from NIH staff to Committee staff, NIH stated:

"Where have tissue samples sitting in a freezer that have been collected from patients in an intramural trial, whom do these samples belong to? Still belong to the donor? NIH? Lab scientist? Government? If it does not belong to the government, want explanation of why not.

Tissue samples collected within the intramural program belong to the Federal Government."

with Dr. Sunderland or any other scientist without a private contract that contained two critical clauses: confidentiality and the right of Pfizer to all intellectual property created as a result of the collaboration.

In a CRADA, Pfizer would not have retained exclusive rights to the data or any patents. Dr. Sunderland would have been precluded from any outside income from the collaboration, if there had been a CRADA such as the one he had executed with Abbott Labs in 1989 in transferring 115 spinal fluid samples. (Exhibit 28)

In this regard it is important to note that Dr. Sunderland is listed as a co-inventor with Pfizer researchers on patents filed in Europe and here in the US relating to the April 1998 MTA.[13] (Exhibit 29) Dr. Sunderland executed at least one assignment of his patent rights to Pfizer as did his co-inventors as was required by his contract of June 10, 1998, and as is typical of discoveries made while on a private payroll. (Exhibit 30) The United States is not an assignee.

In 1997 Pfizer entered into a collaboration with a British firm, Oxford Glycosciences (OGS), to identify unknown biomarkers that would signal the onset of Alzheimer's disease using a proprietary OGS proteomics technology. Dr. David Friedman, the lead Pfizer researcher on the project, began courting Dr. Trey Sunderland in an attempt to obtain access to the NIH human tissue samples in the fall of 1997.

In his interview with Committee staff, Dr. Friedman said he came to understand the significance of the depth of Dr. Sunderland's expertise in his early discussions. On February 20, 1998, Dr. Friedman, and three other Pfizer scientists visited Sunderland's lab at NIMH. A Pfizer e-mail documenting the visit stated: "In discussions regarding Pfizer's needs and Sunderland's needs, Trey indicated that he was very happy with an MTA arrangement plus consulting that Kathy [Smith] has been discussing. Trey was also very interested in publication in a reasonable time frame and that he wanted to make sure that authorship would be based on scientific and intellectual contributions. We indicated agreement on both matters."

A month later, at the suggestion of Dr. Sunderland, Kathryn Monaghan (now Smith), a Pfizer manager, called Kathy Conn, the tech transfer official at NIMH, about using an MTA to transfer spinal fluid samples. Ms. Monaghan believed that this phone call reflected NIH's agreement to proceed with the material transfer agreement and that they can "work out the CRADA vs. Consult part in due course." (Exhibit 31)

On April 6, 1998 Kathy Monaghan faxed the final version of the MTA to Dr. Sunderland and informed him that the deal with OGS had been finalized. (Exhibit 2) However, Ms. Conn informed the Committee staff that she was unaware that the final MTA had been executed.[14] Records and Committee staff interviews of the individuals involved revealed that neither the Director of NIMH nor the NIMH Scientific Director, the two supervisors of Dr. Sunderland, had knowledge of the transfer of the uniquely valuable samples or were informed of the MTA negotiations. On April 8, 1998, Dr. Sunderland signed the MTA to transfer coded clinical samples of spinal fluid and the accompanying data from over 250 subjects to Pfizer. Six days later, Dr. Barrie Hesp signed the MTA for Pfizer.

In a letter dated April 20, 1998, Pfizer sent Dr. Sunderland at NIH the signed copy of the MTA with a note that indicated that they expected the samples to be shipped mid-May (Exhibit 1) Dr. Sunderland was then sent a "draft consulting agreement" to his home in a letter dated on the same day. (Exhibit 5) A two-year consulting agreement that Pfizer labeled the "OGS" agreement was signed by Dr. Hesp (dated June 10, 1998) and Dr. Sunderland (dated June 18, 1998) effective May 1, 1998. (Exhibit 7) It provided for a

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[13] Committee understands from NIH that the NIH has recently made a referral to the OIG-HHS on this issue of undisclosed patent applications.

[14] As discussed later, Ms. Conn believed that the next step in the process was Pfizer sending her a copy of the MTA to review. This matter is discussed in more detail later in the report.

consulting payment to Dr. Trey Sunderland of $25,000 per year and $2,500 per day for each meeting plus expenses. This agreement was renewable for two-year periods, and was renewed two more times.

It should be noted that this consulting agreement required that Dr. Sunderland transfer any interest he may have in the research arising from the agreement with Pfizer as he subsequently did with the patent assignment. (Exhibit 7) Dr. Sunderland also agreed not to "disclose confidential information for so long as it remains unpublished…"

Only after the consulting agreement was signed were the samples finally shipped from NIH. According to Dr. Friedman in his interview with Committee staff, on or around June 24, 1998, Drs. Friedman and Sunderland accompanied 621 tubes to OGS in Britain. But Dr. Sunderland did not deliver the clinical data associated with the samples until August 1998. Emails indicate Pfizer officials were quite upset about the delay because the associated clinical information made these samples useful for the intended research and this delay would affect the pace of the research. (Exhibit). Pfizer calls this research project involving NIMH and OGS the "unknown biomarkers" project.

By the end of July 1998, Pfizer and Sunderland decided to pursue a second collaboration regarding the validity of already "known biomarkers," a beta and tau. (Exhibit 8) The NIH spinal fluid samples were to be used for this project as well. This second project resulted in a second separate consulting agreement for Dr. Sunderland but not a new MTA for the transfer of NIH samples for this separate and new Pfizer research project. The second consulting agreement was signed by Dr. Hesp for Pfizer with an October 6, 1998, date and by Dr. Sunderland with an October 12, 1998, date. On February 9, 1999, the shipment of spinal fluid samples from NIH to Pfizer for the "known biomarkers" project began.

According to records and information, approximately 3,200 tubes of spinal fluid and 388 tubes of plasma were shipped to Pfizer in connection with both biomarker projects.[15] (See Slide 5) Of these, 2,200 or so were for the "known biomarkers" project and the remaining 1,100 were for the "unknown biomarkers" research. The spinal fluid samples linked with the well-characterized clinical data are invaluable tools for scientific research. Based on available records, the NIH only had data on the 2,132 tubes shipped in connection with the "known biomarkers" project. The Committee staff has reasonable grounds to conclude that NIH did not have knowledge of the more than 1,000 tubes of spinal fluid shipped pursuant to the "unknown biomarkers" agreement.

Question Two: Does the available evidence provide reasonable grounds to believe that Dr. Sunderland and others omitted important information, or provided inaccurate information, about the circumstances surrounding Dr. Sunderland's collaborations with Pfizer, Inc. that involved the human samples provided by Dr. Sunderland?

Finding/Supporting Evidence: Yes. While Dr. Sunderland refused invitations to be interviewed by the Committee, records and interviews provide reasonable grounds to believe that some of Dr. Sunderland's statements to the investigators from the Office of Management Assessment and communications from Dr. Sunderland's attorney to NIH were factually inaccurate or incomplete, especially statements relating to the nature of the Pfizer collaborations involving human tissue samples.

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[15] According to Pfizer records, what remains of the samples represents about half of what was shipped by Dr. Sunderland. Pfizer is "happy to work with NIH to arrange the return of the samples." June 6, 2006 e-mail from Daniel Kracov, Esq. (outside counsel to Pfizer) to Committee staff.

Discussion:

The Office of Management Assessment (OMA) of the NIH interviewed Dr. Sunderland regarding these matters on August 19, 2004. Dr. Sunderland signed the interview notes on August 31, 2004, confirming with an "X" that "[t]hese notes, with indicated changes, accurately summarize the interview." (Exhibit 14) Dr. Sunderland informed OMA that while he had taken the required ethics courses and understood there were rules governing disclosure of financial interests and approval of outside activities "he may not have paid proper attention" to such matters in the past. He maintained that he did provide the documents from which to complete the 520s (outside activity request forms) but that somehow the clerical staff did not make the necessary submissions nor did they inform him that such submissions were not made.

With regard to his financial disclosure forms, Dr. Sunderland placed blame for at least part of their inaccuracy on his support staff. The OMA dismissed this argument: "Dr. Sunderland violated NIH and Commissioned Corps procedures and policies on multiple occasions (Pfizer reported 140 activities for which there were no approvals) all of which cannot be dismissed as administrative oversights or anomalies. Given that he acknowledges that he had concerns about administrative support, he should have ensured that forms were submitted to the NIMH ethics office and that approvals were given. Dr. Sunderland was aware of the NIH ethics process through ethics training and was ultimately responsible for ensuring that all activities were approved and all financial disclosures were made." (See Exhibit 32) Committee staff interviewed several individuals within the Geriatric Psychiatry Branch run by Dr. Sunderland and found no support for his position regarding clerical malfeasance.

When asked about his consulting conflicts of interest, Dr. Sunderland told OMA that "he had a consulting arrangement with Pfizer Corporate and the MTA with Pfizer researchers." In fact, not only was the MTA and his initial consulting agreements signed by the same Pfizer official, Dr. Barrie Hesp, both contracts covered work directly related to the samples initially supplied under the MTA. (Exhibit 13)

Dr. Sunderland further claimed that he sent human spinal fluid samples to Pfizer as he had to more than 30 other collaborators and that his collaboration with Pfizer would not have required visits to the company, as this was "an exchange of material for analytical data." In fact, records show that Dr. Sunderland and his associate Karen Putnam visited the Pfizer facilities on a number of occasions to work on the data and, according to Dr. Friedman, at least once Dr. Sunderland accompanied Friedman and the spinal fluid samples on a plane to OGS in England. In addition to the Friedman interview information and several e-mails discussing trips to Pfizer in relation to the unknown biomarker work, both Karen Putnam and Pfizer informed Committee staff that Pfizer considered the primary data associated with the unknown biomarker project to be proprietary and could only be accessed on Pfizer property. (Exhibit 33)

Another inconsistency with the relevant documents and the information conveyed by Pfizer regarding Dr. Sunderland's consulting activities was Dr. Sunderland's statement in the OMA interview that "his consulting work with Pfizer has to do with drug development and lectures." Certainly lectures to audiences of doctors arranged by Pfizer's marketing team charged with promoting Aricept accounted for substantial payments to Dr. Sunderland ($311,150 from 1996 to 2004 according to Pfizer) (Exhibit 34) The consulting work involving the human tissue samples, however, was separate and apart from those lectures. (Exhibit 34) To the extent Dr. Sunderland meant that his "drug development" consulting was drug-specific, except perhaps for participation on various Pfizer-sponsored Advisory Boards relating to marketing strategy, Committee staff found little evidence from records or interviews that Dr. Sunderland's consulting with Pfizer was related to any existing drug or drug under development. On the other hand, if Dr. Sunderland meant that his "drug development" consulting in a more general way applying to strategic advice to classes of medications, his attorney in a December 8,

2004, letter to NIH distinguished this general consulting from his work on the "unknown biomarkers" project: "Generating new approaches to shorten the duration of clinical trials using various target markers is an obvious priority for companies like Pfizer, and Dr. Sunderland provided ongoing consultation about the development of such strategies. This consulting is quite different and separate from the exploration of *peptide biomarkers* for possible diagnostic and prognostic use in Alzheimer's disease."[16] (Emphasis added). Later in the same letter, Dr. Sunderland's attorney described a reason for the April 1998 MTA collaboration as "[p]roteomic exploration of CSF [cerebrospinal fluid] was designed to help discover *peptide targets* for drug development with both scientific and potential commercial applications."[17] (Emphasis added).

During much of the time period (1998-2004) of Dr. Sunderland's consulting with Pfizer, Ms. Karen Putnam was a 32-hour per week employee of NIMH assigned to Dr. Sunderland's branch, although she was telecommuting from the University of Cincinnati where she was pursuing a graduate degree. (See Exhibit 11) According to e-mails, Dr. Sunderland urged Pfizer to hire Ms. Putnam to administer the database related to the unknown biomarker project. Pfizer tightly held the data from this "collaboration" so her work on that database had to be done at the company. Ms. Putnam performed a similar function with regard to the "known biomarkers" database. She informed the Committee staff that she understood that while the "unknown biomarkers" project was covered by her consulting agreement with Pfizer, the work she and Dr. Sunderland did with Pfizer on known biomarkers was a part of her official duties. Both biomarker projects started with consulting contracts between Pfizer and Dr. Sunderland, not independently and solely from NIH.

During his OMA interview Dr. Sunderland was asked whether he told Karen Putnam that she did not have to seek approval for her work with him at Pfizer. In the signed interview notes Dr. Sunderland claimed not to remember if he told Ms. Putnam not to file, but he went on to state that he did not think she had to because she was a part-time employee on an IPA and because "her duties did not overlap with any decisions regarding drug or protocol development." Ms. Putnam was a direct report to Dr. Sunderland and had received almost $65,000 in consulting fees and expenses from Pfizer to manage the data of the unknown biomarker study. (Exhibit 39). OMA found, and Ms. Putnam confirmed, that she had not submitted requests for outside activities. Exhibit 11. In addition, the NIH ethics review panel concluded that had Karen Putnam filed a request for outside activity the request would have been denied because it related to her official duties. (Exhibit 27) OMA noted in its review of Karen Putnam's outside activities that in an e-mail to Ms. Putnam, dated June 18, 2004, the NIMH Ethics Coordinator stated that Dr. Sunderland had called from abroad to say that he had advised Ms. Putnam that she did not have to file for prior approval.

Dr. Sunderland's attorney in an August 31, 2004, letter to OMA stated: "There was no conflict between his consulting/lecturing and his clinical work at the NIH. . . "[He] never hid that relationship; and that there never was a conflict of interest – in any respect whatsoever – between his NIH work and what he did as a consultant and speaker for Pfizer. . . . The relevant facts are now before the NIH in their entirety." The NIH Ethics Review Panel specifically found that there was "a direct overlap between the subject matter of Dr. Sunderland's official area of research and the scientific subject matter of his Pfizer consultancies." (Exhibit 35) He would not have been "given prior approval for the consultant activities." The Ethics Panel "expressed further concern over the Material Transfer Agreement (MTA) that Dr. Sunderland entered into with Pfizer in 1998 while he maintained an ongoing consulting relationship with the company in the same area."

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[16] December 8, 2004, letter from Robert F. Muse, Esq. to Holli Beckerman Jaffe, Director, NIH Ethics Office, page 7.
[17] Id. , page 8.

Based on records and interviews, Committee staff believes that NIH did not conduct interviews with Pfizer employees nor obtain from Pfizer the underlying records of Dr. Sunderland's consulting agreements. Thus, even without the Pfizer documents and interviews that show connections between the MTA and the consulting, the Ethics Review Panel still concluded in April 2005 that there was a conflict of interest.

Moreover, OMA believed that Dr. Sunderland did much of the Pfizer-paid work on government time. Dr. Sunderland acknowledged in the OMA interview that he never kept track of his leave time nor, as her supervisor at NIH, did he check to see if Ms. Putnam had taken leave when he signed her time cards.

Records and interviews also raised questions about Dr. Sunderland's openness about the "unknown biomarkers" consulting agreement involving a third-party British company called OGS. For example, in her June 9, 1998, e-mail, Kathryn Smith noted to other Pfizer officers: "For your information, Dr. Trey Sunderland at NIH (our source for the AD samples) has requested that we do not mention him in any publicity concerning his involvement in our OGS collaboration." (Exhibit 23). In addition, when the Committee first raised questions about the discrepancies involving Dr. Sunderland's outside activities with Pfizer, the NIMH ethics coordinator in a June 18, 2004 e-mail to Dr. Sunderland asked directly: "There is a record of an MTA agreement with Pfizer signed 4/98. Could payments have related to that?" (Exhibit 16) Based on records and interviews, there is no evidence that Dr. Sunderland responded to this question. It should also be noted that the terms of Dr. Sunderland's consulting agreements state: "Pfizer agrees that it will not make public this agreement nor the terms associated with it."

Dr. Trey Sunderland is still an employee at the NIMH and is a member of Public Health Service Commissioned Corps. Administrative action rests with the Corps and not NIH per se. Dr. Thomas Insel, the Director of NIMH, forwarded a summary of the OMA findings and those of the Ethics Panel to the Commissioned Corps, noting that he was informed that civilian employees guilty of the same violations would be proposed for removal. In relevant part that document states:

> "Dr. Sunderland placed the NIH in a position where it had to respond to allegations of impropriety, which compromised faith in the Agency and trust in our research.
>
> Dr. Sunderland violated ethics rules with regard to his relationship with Pfizer and engaged in relationships with Pfizer and many other organizations that would not have been approved had he submitted them for approval in accordance with the process for seeking approval of outside activities…Not disclosing over $500,000 in income was not an oversight or lapse in judgment but appears to be a deliberate decision not to comply with the rules, policies and procedures that are necessary to protect the NIH, its scientists and most importantly, its science."

Question Three: Did the Committee's investigation of the circumstances surrounding Dr. Sunderland's transfer of human samples to Pfizer identify evidence that raised other compliance issues and policy questions?

Finding/ Supporting Evidence: Yes. The investigation found reasonable grounds to believe there was questionable compliance with human subject protection and NIH technology transfer policies that existed at the time. The evidence also raised regulatory and ethical questions that are pertinent to NIH's consideration of current policy related to human tissue samples.

Discussion:

Human subject protection

A human subject is a living individual about whom a researcher (called an investigator) obtains either (1) data through intervention or interaction with the individual, or (2) identifiable private information.[18] In the case study before the Subcommittee, Dr. Sunderland and other researchers collected spinal fluid by injecting the human subject with a needle at the base of the spine in a procedure called lumbar puncture (LP). According to the informed consent language in several of the protocols involved, this procedure is conducted in the morning, after the subject has had a night of bedrest. The subject lies on one side, the subject's lower back is cleaned with antiseptic, and a local anesthetic such as novocaine is injected in order to temporarily numb a small area of skin. A needle is then placed into the spinal fluid sac, allowing an ounce of spinal fluid to drip into collection tubes. The needle is then removed and the subject is asked to lie on her/his abdomen for three hours to reduce the likelihood of developing a headache after this procedure. The LP procedure only takes 5-15 minutes. Most subjects experience only minor or moderate pain, similar to that experienced when an injection is received.

The spinal fluid samples, usually collected in 20-30 cc amounts, are then alliquotted or subdivided into ten smaller tubes. Some small subset of the total amount is then used for the research study, with several other vials or test tubes of fluid left over, unused, stored in –70 degree centigrade freezers.

Researchers at the NIH are responsible for protecting the rights and welfare of the human subjects who participate in their research. All intramural researchers at the NIH are responsible for knowing whether or not their research involves human subjects. Thus, legal obligations to protect human subjects apply to human tissue samples and private information, such as medical information, that can be readily identified with individuals.

a. Questionable handling of informed consent. One issue presented by this matter involves the adequacy of informed consent for new, future uses of leftover human samples. The ethical foundation for informed consent is the principle of respect for persons, which requires that research subjects be given the opportunity to choose what shall and shall not happen to them.[19] Valid informed consent requires disclosure of relevant information about the research, comprehension of the information by the prospective subject, and his or her voluntary agreement, free of coercion and undue influence, to participation.[20]

In this case, Dr. Sunderland transferred spinal fluid samples to Pfizer that were collected from subjects whom most were told of the specific purpose of the particular research study being conducted, but not about the research purpose of the Pfizer collaboration, because in many cases that collaboration had not yet even been developed. At the time of collection, many of the spinal fluid samples were not obtained for the research purpose of the Pfizer collaboration. In general, there is a question about whether most of the protocols at issue had adequate informed consent language about consenting for future research uses of leftover samples.[21] A few of the protocols involving the

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[18] Title 45 Code of Federal Regulations, Part 46.

[19] National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research. The Belmont Report: ethical principles for the protection of human subjects of research. Washington, D.C.:Government Printing Office, April 18, 1979. U.S. Department of Health and Human Services publication GPO 887-809.

[20] Position Statement, The Ethics and Humanities Subcommittee of the American Academy of Neurology, Neurology 1998, 50: 592-595.

[21] That silence or ambiguity would not have been unusual for most clinical research protocols because there had been no requirement to address future uses. It was not until January 2006 that the NIH Office of Human Subjects Research (OHSR) explicitly addressed this issue, revised its

subjects are still ongoing and Dr. Sunderland actually sought Institutional Review Board (IRB) approval for amending these ongoing protocols to reflect the new research purpose involving Pfizer.

Human subject protection regulations, however, state that unless the samples are anonymized and not linked to identifiable patients, the human tissue samples are not exempt from IRB review and some independent review (either from the IRB or the human subjects protection office of the institute or center) must be conducted to determine if full IRB review is needed and if so, whether the subjects need to be consented again for the new use.[22] With respect to the samples transferred to Pfizer, NIH reported to Committee staff by e-mail that "[n]either the NIH OHSR [Office of Human Subjects Research] nor the NIMH [Institutional Review Board] have records documenting a review of the transfer to Pfizer." According to NIH, "Dr. Sunderland has advised NIH that he believed at the time of the transfer that use of specimens in his collaboration with Pfizer, as described in the 1998 MTA, was completely consistent with both the protocols in which those samples were obtained, and the informed consent documents signed by participants."

But was it Dr. Sunderland's judgment alone to determine whether the use of the samples was consistent with the protocols? Under the April 1995 Guidelines for the Conduct of Research Involving Human Subjects in effect at the time of the 1998 transfer, the use of human tissue samples were exempt from the NIH requirements on human research protection if the sources of pathological specimens "cannot be identified directly or through identifiers linked to the subjects." The Guidelines also state in bolded print: "Investigators should not make determinations about exemptions without consulting OHSR."

The terms of 1998 Material Transfer Agreement (Exhibits 2 and 3) and the records produced by Pfizer relating to the samples provide reasonable grounds to believe that Dr. Sunderland intended to transfer, and actually transferred, coded clinical samples to Pfizer. Coded clinical samples are specimens supplied with a code rather than a name or social security number. Because these samples remain linked through codes to identifiable subjects, questions are raised over whether these samples would have been covered by human subject protection guidelines and whether Dr. Sunderland should have sought an independent consultation or determination.[23] Currently, in light of concerns raised by the Committee's investigation and at the direction of the NIH Deputy Director for Intramural

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guidance, and issued "Sheet 14 Guidance on the Research Use of Stored Samples or Data." In that guidance, researchers are required to submit a written protocol to an NIH IRB that includes a description of how samples will be tracked, how samples will be stored to be protected from loss or destruction, plans for samples at the conclusion of the protocol, and what circumstances would cause the lead researcher to report a loss or destruction of samples to the IRB. In discussion with Committee staff, the NIH Deputy Director of Intramural Research, whose office includes OHSR, stated that this revision occurred in response to the Committee's investigation.

[22] David B. Resnik, J.D., Ph.D., National Institute of Environmental Health Sciences (NIEHS) Bioethics Bulletin, "Human Research Q&A," Spring 2005, at 2:

Question: "I have access to some leftover tissue samples from another investigator's work. I would like to conduct some research on these samples. Is this research on a human subject? Do I need to submit a protocol to the NIEHS's Institutional Review Board (IRB)?

Short answer: This is not research on a human subject but you still need to contact the IRB before using these samples in research, since the samples were taken from human subjects."

[23] After several months of inquiries by Dr. Molchan, Dr. Sunderland sent 0.5 cc paired spinal-fluid samples from eight Alzheimer's disease patients and two elderly normal volunteers to an outside researcher. In his interview with Committee staff, the Director of NIMH raised the issue of whether this transfer was in compliance with NIH guidelines along the same lines that questions had been raised by Dr. Sunderland's transfer of samples to Pfizer. Dr. Molchan, however, told the Committee staff that the research purpose of the outside researcher was the same purpose (to conduct a lithium study) in the study she had not been able to complete.

Research, an NIH investigation is being conducted to determine if Dr. Sunderland violated any regulatory or ethical standards in transferring spinal fluid samples to Pfizer without any IRB review from protocols that did not cover the research purpose in the Pfizer biomarker projects.

b. Inadvertent disclosure of subject names and other privacy information. In reviewing records produced by Pfizer, Committee staff found that February-March 1999 spreadsheet records for assays of two different potential biomarkers in 1999 contained the names of approximately 120 subjects who were the sources of the biological material, along with their codenames, NIH ID numbers, dates of birth, race, and sex. In consultation with Pfizer's outside counsel, Committee staff confirmed that these records did indeed represent an inadvertent disclosure of subject names. According to Pfizer's outside counsel in a March 31, 2006, letter to Committee staff, the spreadsheets contained information transcribed by Pfizer from labels on the vials sent by the NIMH. The samples were subsequently coded by Pfizer for analysis using the first three letters of the patient's last name followed by the first three letters of the first name. The results of the study were included in the April 23, 2003, article in the Journal of American Medical Association as well as the analysis of a later set of samples. Subsequent samples arrived from the NIMH pre-coded using a numerical coding system.

In response to the Committee staff's question about Pfizer's handling of this inadvertent disclosure, Pfizer's outside counsel wrote:

"At the time that the NIH disclosure occurred, the Health Insurance Portability and Accountability Act (HIPAA), which established requirements regarding the use and disclosure of Protected Health Information, was not yet in effect, and thus there was no legal obligation imposed upon Pfizer to return or reject the information received. Even under the current HIPAA requirements, Pfizer's research and development organization is not a 'covered entity,' and the duties imposed on such persons inadvertently receiving protected information are not clear. However, we believe Pfizer handled the inadvertent disclosure appropriately by creating an [sic] code to de-identify patients in the course of the research effort."[24]

There is no evidence that Pfizer contacted NIH about the inadvertent disclosure. There is no evidence that NIMH was aware of the inadvertent disclosure. If that was the case, NIH had no information to determine what led to the inadvertent disclosure, and was not in a position to correct a possibly recurring, systemic problem that increases the risk of inadvertent disclosure of privacy information. Further investigation would be needed to determine the circumstances that led to the inadvertent disclosure.

Committee staff understands from a discussion with NIH Acting Director for Human Research Protection that the release of patient names, whether accidental or not, is not consistent with NIH research standards and any manuscript in connection with the affected research project might not be published. This would need to be reported to the IRB, and to the NIH Deputy Director for Intramural Research. The NIH Deputy Director in turn might report this disclosure to the Office of Human Research Protection.

c. Questionable non-disclosure of financial relationship to IRB. As part of his financial arrangement with Pfizer, Dr. Sunderland transferred spinal fluid samples to Pfizer from 1998 to 2004 for which he was paid $285,000 to advise Pfizer on data relating to the samples provided. According to NIH records, Dr. Sunderland provided

[24] Letter dated May 10, 2006, from Daniel A. Kracov, Esq., Arnold & Porter (on behalf of Pfizer, Inc.) to Committee staff.

spinal fluid samples that had been collected from 14 different studies.[25] Two of these studies were initiated in 2001 and 2002, respectively. In other words, Dr. Sunderland was performing lumbar punctures for spinal fluid at a time Pfizer wanted spinal fluid samples, and at a time Dr. Sunderland sought and received monetary compensation for his efforts to assist Pfizer in interpreting data generated from these spinal fluid samples he provided. In addition, while other studies no longer involved active collection of spinal fluid, these studies were still ongoing and were subject to continuing review by the NIMH IRB. As part of this continuing review process, Dr. Sunderland as the accountable investigator on the study had to check off "yes" or "no" responses to a series of questions on the NIH-1195 form, Clinical Research Protocol Continuing Review Application. The last question on the form was: "Have any investigators developed an equity or consultative relationship with a non-NIH source related to this protocol which might be considered a conflict of interest?" According to all forms related to spinal fluid protocols signed by Dr. Sunderland during the time he was consulting with Pfizer, the "no" box response was checked. (Exhibit 24)

Committee staff did not receive any records that linked the individual samples provided to Pfizer to specific protocol numbers. The 2001 study and the 2002 study, however, were identified as sources of spinal fluid samples to Pfizer. (Exhibit 26) Thus, while the Committee staff does not believe it has records linking the protocol number to a particular NIMH shipment to Pfizer, samples were provided to Pfizer from these studies in one of those years in which Dr. Sunderland represented to the IRB that he (or any other investigator associated with the study) had no outside financial interests related to the protocol.

d. Cancellation of lithium study without notice to subjects. Dr. Molchan left NIMH in early 1997. By that time, Dr. Molchan had completed the spinal fluid collection phase of the lithium study a few years earlier. She was still, however, conducting the study and had used only a relatively small percentage of the samples.

Committee staff understands that sometimes when an NIH scientist in charge of a human subjects study leaves NIH, another NIH scientist is assigned to take charge of the study and the study is continued.[26] When Dr. Molchan left NIMH, there was reason to believe (IRB approval, two papers published) the lithium study would be continued and that Dr. Sunderland as Branch Chief would either take over the study or assign someone to take over the study. Instead, the study was discontinued. Committee staff has asked NIH why the study was discontinued. To date, NIH has not provided a response on why this study was discontinued.

Committee staff has not found any evidence that the subjects in the lithium study were notified about the termination of a study. In these cases, where a clinical trial is terminated, the question is raised whether the subjects in that study should be notified of the termination. It is unclear how common it is for the written protocols of the clinical trial to include provisions about termination and notification. On the question of when a subject should be notified about termination of a study, an NIH official with expertise on human subjects protection told Committee staff that she believed that it depended on whether the study followed the subjects over a period of time. Nevertheless, the NIH Office of Intramural Research is working on a computer consent prototype and whether it should be a standard requirement to inform subjects of a study's termination.

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[25] The NIH recently advised the Committee staff that the internal NIH investigation on human subject research issues had identified 16 different studies connected to Dr. Sunderland's transfer of human samples to Pfizer.

[26] For example, in 2005 Dr. Robert Cohen took over as the Principal Investigator for Dr. Sunderland in a few of the protocols involved as sources of spinal fluid for Pfizer.

Technology Transfer Issues

In pursuing its mission, NIH scientists often discover new technologies. The process of sharing these new technologies with other organizations and the public is called technology transfer. For example, the sharing of new research materials with colleagues, the pursuit of collaborative relationships with outside entities, and the awarding of intellectual property rights to commercial entities for development and commercialization, are all considered technology transfer activities. The NIH Office of Technology Transfer is responsible for developing and implementing technology transfer policies at NIH. Each Institute has a technology transfer office that monitors, evaluates, and manages the Institute's invention portfolio. These offices review Employee Invention Reports (EIRs) and negotiate transactional agreements between the Institute and outside parties, including other Federal laboratories, State and local governments, universities, and pharmaceutical and biotechnology companies. Among these agreements are Material Transfer Agreements (MTAs) for the exchange of research materials, and Cooperative Research and Developments Agreements (CRADAs) for collaborative research endeavors.

In this case, questions are raised in a number of areas about how NIMH at the time implemented technology transfer policies and the adequacy of certain technology transfer policies.

a. Improperly authorized transfer. The transfer of spinal fluid samples was facilitated by the April 1998 Material Transfer Agreement between NIMH and Pfizer. The Committee's investigation found two versions of the executed MTA. One version contained the signature of Dr. Sunderland as the provider of the samples on behalf of NIMH and the signatory for Pfizer, Dr. Barrie Hesp. (Exhibit 3) This is the only version of the MTA that Pfizer told the Committee staff it has. Committee staff found no evidence that Pfizer had any other version of the MTA. According to a Pfizer manager involved with the MTA, Pfizer made an effort to confirm that Dr. Sunderland had the authority.[27] A March 1998 Pfizer e-mail does substantiate phone contact between the Pfizer manager and the NIMH technology transfer director about the MTA.[28] Although she did not have specific recollection about the Pfizer phone call, the NIMH technology transfer director at the time (who has since left the NIH) told the Committee staff that she recalled getting phone calls about MTAs. These would not have been calls to receive official clearance but just preliminary inquiries. These kinds of calls were not documented. According to the official, she believed the Pfizer inquiry would have been about what form to use in transferring samples to Pfizer. She did not know that Dr. Sunderland and Pfizer were executing the MTA immediately. She expected to see the MTA and review it. There is, however, no evidence showing she received any Pfizer correspondence and was sent the MTA. She had no recollection about any mention of possible consulting, but even if it had been mentioned, she would have expected the ethics office to be involved in that review. The official disputes that she confirmed that

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[27] May 10, 2006, letter from Daniel Kracov, Esq. to Committee staff: "In April 1998, what was Pfizer's understanding of Dr. Sunderland's authority to sign an MTA? In 1998, Pfizer sought to confirm Trey Sunderland's authority to enter into the MTA on behalf of NIH. In this regard, Pfizer's Kathy Smith was referred to Kathy Conn at NIH [the NIMH Director for Technology Transfer] who, to Kathy Smith's recollection, confirmed that Dr. Sunderland was authorized to execute the agreement. It has been Pfizer's standard practice when dealing with academic institutions, including institutions such as NIH, not to accept an investigator's claim to have authority to sign an agreement without consulting with an appropriate representative of the contracting institution."

[28] E-mail from Kathryn E. Monaghan [Smith] to Trey Sunderland, March 24, 1998: "Trey, I spoke with Kathy Conn today and she also reconfirmed that we can proceed with the MTA immediately and work out the CRADA vs. Consult part in due course. I fedexed various forms of the MTA on Friday -- hope you got them yesterday?" Exhibit 31.

Dr. Sunderland was authorized to execute the agreement. Based on the phone call, the official expected to review the MTA and forward it to the NIMH Scientific Director for signature. The official's recollection was that all transfers of human tissue samples to researchers outside NIH were documented through MTAs.

In early 1999 during an office move, the NIMH technology transfer office staff discovered a number of MTAs that had not been co-signed by the NIMH Scientific Director, as required by the written delegations of authority in effect at the time. One of these MTAs was the Sunderland-Pfizer MTA. When these MTAs were brought to his attention, the NIMH Scientific Director co-signed. He co-signed the Pfizer MTA on February 24, 1999. At that time, NIMH had already made three shipments of spinal fluid to Pfizer. (Exhibit 3, p.3) The co-signed MTA was retained in NIMH files. According to NIH, there was no evidence that Dr. Sunderland was given a copy of the 1998 MTA after Dr. Desimone signed, and Dr. Sunderland told NIMH he did not get a copy of the co-signed MTA until about several months ago when he requested it from the NIMH Executive Officer.[29] Moreover, it is unknown when Dr. Sunderland learned about the existence of the co-signed MTA.

The available evidence shows that Pfizer only had the MTA with Dr. Sunderland's signature. Under NIMH policy at the time, however, Dr. Sunderland was not the authorized signatory to execute the MTA. Questions arise about whether NIMH's transfer of samples was legally authorized and the legal implications for NIH. Furthermore, available evidence shows that NIMH management did not provide the co-signed versions to either Dr. Sunderland or Pfizer. This is of concern because NIMH management should have an interest in correcting an internal problem of unauthorized or improperly authorized material transfers. The problem cannot be corrected if management does not make NIH scientists aware of the error. In a conversation with Committee staff, the former NIMH technology transfer director acknowledged that this was an oversight.

b. Plasma samples transferred without MTA. According to records from Pfizer and others, NIMH shipped 388 plasma samples to Pfizer on August 19, 2002. The Committee has no records of a material transfer agreement covering these plasma samples. The April 1998 MTA and the October 6, 2000, amendment to this MTA only covered coded clinical samples of spinal fluid and serum.[30]

c. Questionable amendment to MTA. The April 1998 MTA was executed using the Public Health Service Agreement MTA form and Dr. Sunderland was listed as the provider at his NIMH address. The October 6, 2000, amendment to the April 1998 MTA was executed on Pfizer letterhead and listed Dr. Sunderland at his home address. Committee staff asked NIH whether there were any amendments to the 1998 Pfizer MTA. NIH told the Committee staff that the NIMH Technology Transfer Office did not have an amendment but then NIMH asked Dr. Sunderland if there had been any amendments. At that point, Dr. Sunderland produced the October 2000 amendment. In an interview with Committee staff, the NIMH Technology Transfer Director stated that this amendment "would have raised eyebrows." Even though NIH told the Committee staff that Dr. Sunderland had the signatory authority to execute an MTA in 2000, because Dr. Sunderland had executed the MTA and had it co-signed by the NIH Scientific Director, the same process of authorization in effect in 1998 should have been used for the amendment in 2000.

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[29] E-mail from Gemma Flamberg (NIH) to Alan Slobodin (Committee staff), June 1, 2006. (Exhibit 37)

[30] Pfizer, however, did not actually receive any serum from NIMH (March 31, 2006, letter from Daniel A. Kracov, Esq. to Committee staff).

d. NIMH policy on MTAs lacked basic controls of accountability. According to an NIH e-mail to Committee staff, Dr. Sunderland had the authority to transfer the spinal fluid samples to Pfizer on his own without any approval or reporting, as long as Dr. Sunderland chose not to document the transfer without an MTA. Because he chose to execute an MTA, however, he did not have authority on his own to provide the samples. He needed clearance from the NIH Scientific Director. In other words, NIMH policy at the time, as represented by NIH, gave scientists more authority to provide government property to non-government researchers without any paperwork than if the scientists chose to do the paperwork. This kind of system raises the question whether such a policy incentivized a lack of accountability.

Moreover, in 1999 the NIMH changed its written delegations of authority to permit Branch Chiefs, such as Dr. Sunderland, to have sign-off authority on MTAs. The stated rationale was to ensure that branch chiefs were aware of what materials were coming and going from the labs under their supervision. According to NIH in an e-mail to Committee staff, Dr. Sunderland had the authority after May 24, 1999 to approve his own transfers of material (including human tissue samples) outside NIH. This NIMH policy, or perhaps policy interpretation, raises the question about the lack of essential checks and balances to protect against fraud and error because the Branch Chief could approve his own MTAs for samples from studies in which he was involved as the Principal Investigator.

e. Lack of clarity in NIMH policy on MTAs. Committee staff found an information bulletin, "NIH Technology Transfer and You," posted on the NIMH Technology Transfer Office (TTO) web site. The bulletin stated that that the NIMH version was revised on February 24, 2000. This bulletin stated in boldface type:

Current NIH policy requires that MTAs be used whenever an NIH scientist sends out or receives materials, e.g., cDNAs, cell lines, antibodies, etc. These agreements must be signed by authorized IC personnel.[31]

The NIMH TTO Director at that time told Committee staff in an interview that MTAs were required. Other NIMH officials and NIH, however, disputed that the policy was so clear-cut. Rather, scientists were encouraged to use MTAs but not required to do so. In other words, MTAs were discretionary. NIMH officials interviewed by Committee staff also were not familiar with the TTO Bulletin. This area raises a question about the adequacy and accuracy of internal communication at NIMH. There is also a question about what was the actual policy.

f. The MTA was a questionable mechanism for the transfer. Committee staff obtained records showing that Dr. Sunderland was the provider of spinal fluid samples in a 1989 Cooperative Research and Development Agreement (CRADA) between NIMH and Abbott Laboratories. Under this CRADA, Dr. Sunderland provided 115 samples of spinal fluid to Abbott. NIH and NIMH officials could not distinguish between the Abbott transfer and the Pfizer transfer in terms of why a CRADA was used with the transfer to Abbott but not with the one to Pfizer in 1998. Moreover, at a 1999 NIH Conference on Biomarkers, Dr. Sunderland stated: "In a large-scale *collaboration* between the NIMH, Pfizer, and OGS, we have embarked on a series of studies focused on one very important part of biomarker puzzle," and later stated that "cerebrospinal fluid markers are the focus of our *collaborative* efforts with Pfizer and OGS."[32] (Emphasis added). Given such

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[31] (Exhibit 38)

[32] T. Sunderland, "Prospective search for Alzheimer's disease (AD) biomarkers," in Downing, ed., Biomarkers and Surrogate Endpoints: clinical research and applications, Proceedings of the NIH-FDA Conference held on 15-16 April 1999 in Bethesda, Maryland, USA, at 39, 40 (Elsevier, 2000).

characterizations[33] of the activity with Pfizer and OGS as well as other information, these officials believe that Dr. Sunderland and Pfizer were in fact engaged in a collaboration in which a CRADA would have been the appropriate mechanism to use.

g. Reference to third-party collaborator in MTA should have triggered more scrutiny. Provision #2 in the April 1998 MTA stated that: "The Research Material will only be used for research purposes by Recipient and Recipient's collaborator in the UK, for the research projects described below, under suitable containment conditions." The mention of the Recipient's collaborator in the UK was a reference to Oxford Glycosciences, Ltd., (OGS), as part of the collaboration with Pfizer. OGS was part of the three-way collaboration with Pfizer and NIMH. OGS used 2D gel electrophoresis techniques to detect proteins in spinal fluid. OGS was not, however, specifically identified in the MTA. The involvement of a third-party collaborator raises a question of whether this was a modification of a routine material transfer and should have triggered further scrutiny from the Technology Transfer Office. The question is raised about whether uses and recipients of samples are adequately reported in the MTA and whether NIMH should have been made more aware of OGS and the use of the samples. Moreover, the MTA authorized the transfer of spinal fluid samples for the narrow purpose of the collaboration, which Pfizer refers to as the "unknown biomarker" projects. Records, however, produced to the Committee show that Dr. Sunderland provided over 2,100 samples to Pfizer for the "known biomarker" project. OGS, however, was not involved in this collaboration and it was actually a separate biomarker research project. A question is further raised whether the 2100 samples sent to Pfizer for this project were entirely unauthorized.

h. Most of the samples transferred to Pfizer may not have been covered by the MTA and the MTA amendment. As mentioned before, the terms of the MTA related to transfers for the research purpose of the three-way collaboration of NIMH, Pfizer, and OGS. Pfizer calls this collaboration the "unknown biomarkers" project. The second project between Dr. Sunderland and Pfizer, did not involve OGS and Pfizer calls this "the known biomarker project." The NIH documents produced to the committee relating to the Pfizer collaboration state that the total number of samples sent to Pfizer equals 2132 vials for beta-amyloid 1-42, beta-amyloid 1-40, and tau. These are known biomarkers and relate to the "known biomarker" project. One of the NIH documents asserts that the samples sent to Pfizer were "through the NIH-approved MTA." The Committee, however, has not received any records of any MTA covering the known biomarker project. It is highly questionable whether NIH technology transfer and legal officials would find that the April 1998 MTA for the unknown biomarker project could be used to authorize transfer for the known biomarker project, even though it involved the same company and the same area of research, because the samples were used for a different research purpose.

Science management concerns

Three important concerns were raised: lack of retention of clinical research data, conflict of interest in committing NIH scientific resources, and NIH oversight of unpublished research.

a. Lack of retention of clinical research data. When Dr. Molchan inquired about getting the leftover spinal fluid samples, she also asked about getting the data from her uncompleted lithium study. Dr. Sunderland informed Dr. Molchan that this data was no longer available:

"Dear Sue,

[33]Dr. Sunderland also highlighted this collaboration in a paper he prepared for a 2000 NIMH of Board of Scientific Counselors review of research in his branch.

Over the last few days, we have been searching electronic files and paper files to see what we could find. Unfortunately, the data is no longer available. Just so you know, we had to go through several purges over the last few years when we moved offices, and anything over 5-7 years old was subject to purging. Since these studies and the resultant publications go back over 15 years in some cases, they were not carried forward to our limited space. . . . " (Trey Sunderland e-mail , March 14, 2005 to Susan Molchan).

Dr. Molchan raised the issue of data retention in an e-mail to Committee staff: "Does NIH have a policy on what happens to data like this when scientists leave the NIH? It seems wasteful to repeat the same studies without having earlier results."

Two senior NIH officials provided somewhat conflicting information. One official confirmed the policy of purging clinical data after seven years. Another official, however, had never heard of such a policy. The Subcommittee may wish to raise this question with NIH about what the policy is, and what the policy should be, on retention of clinical research, particularly in cases where the researcher has left NIH.

b. Commitment of resources. Dr. Sunderland's collaborations with Pfizer resulted in the shipment of over 3,000 spinal fluid and plasma samples. These samples were extraordinarily valuable, both scientifically and commercially, because they contained useful information, they were linked to well-characterized clinical data (lots of medical details about the subjects), and the samples were taken from these same subjects over different points in time over several years. The Committee staff could find no evidence that showed in 1998 any NIMH official besides Dr. Sunderland who was even aware, much less supportive, of the merits of the Pfizer collaboration. Thus, Dr. Sunderland, while having concurrent financial interests with Pfizer, made the decision to commit 3,000 non-renewable taxpayer-supported human research samples.

Techniques employed in proteomic analysis are new and evolving. Even if Dr. Sunderland may have been the scientist in the best position to evaluate whether the OGS technology was promising enough to consume these valuable human tissue samples, the intramural research program at NIMH or NIH may have had more than one expert in proteomics to assist in such a decision. Could Dr. Sunderland's scientific judgment have been better informed by consultations with other proteomic experts at NIH? The Pfizer projects may have been the most promising collaboration available in the search for biomarkers of Alzheimer's disease. Could an exploration of other private sector or academic partners produced a more promising result? Most importantly should a single scientist be the sole decisionmaker about the best use of these unique human tissue samples, especially with direct financial interests involved?

c. NIH oversight of unpublished research. In the year 2000, Dr. Sunderland prepared a document called "Overview - GPB," in preparation for a review by the NIMH Board of Scientific Counselors. On page 3 of this document, the discussion about the Pfizer/OGS collaboration is as follows:

"Perhaps the most interesting interaction is the three-way collaboration between the NIMH, Pfizer, Inc., and Oxford Glycosciences in England. This cooperative approach was first established in 1998 to investigate protein spots in the CSF of AD subjects and 'at risk' controls at baseline and over time. While this convergence of government investigators, the pharmaceutical industry, and a biotechnology firm has been highlighted by the NIH Director at a recent national biomarkers meeting as a way to leverage resources and scientific interest in the future, the proof of its power must come from the data, especially over time. Using high-throughput, exquisitely sensitive 2D gel electrophoresis techniques which provide quantitative data reflecting the up- and down-regulation of proteins in human CSF, we are generating cross-sectional data on over 1200 proteins in groups of AD and 'at risk' subjects. Perhaps most importantly, we will have

longitudinal data in both these groups through repeat CSF collections that will allow us to track protein changes through the evolution of this illness."

Under normal circumstances, the BSC would have been scheduled for another review of Dr. Sunderland's work in 2005. However, because in late 2004, NIMH officials believed that Dr. Sunderland was going to be leaving the NIH the BSC review was cancelled. The Committee staff has not found any publications related to the Pfizer/OGS collaboration. When asked by Committee staff to retrieve data or some kind of workproduct that resulted from this collaboration, NIH was unable to do so. In an interview with Committee staff, Karen Putnam indicated that all data related to the unknown biomarker project was maintained on-site at Pfizer. As Ms. Putnam noted in her December 7, 2004, letter to NIH:

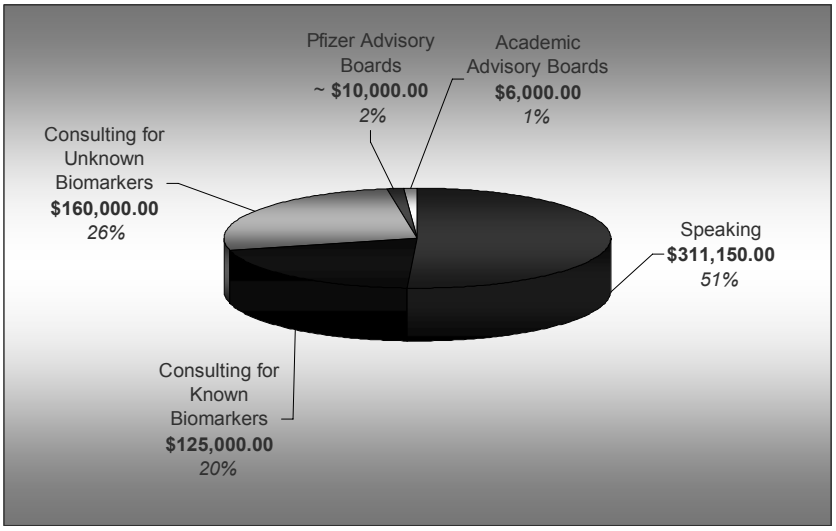
"Pfizer asked me to consult in the fields of statistics and data management. I was involved in specific projects exploring proteomics and statistical methodology. The Pfizer activities centered around discovery research, where the results were used to generate future hypotheses and directions of research. The results generated from my Pfizer outside activities were not part of the data involved in my current government job. All proteomics data were confidential and kept at the Pfizer site. The computer software and hardware used in exploring proteomics data was located at the Pfizer site."

Outside counsel to Pfizer confirmed to Committee staff that this was essentially correct. Thus, the available evidence is that the unknown biomarkers project (or "discovery research" per Ms. Putnam) did not generate data that came into possession of the NIH. Under these particular circumstances, NIH was unable to report to the Committee what this collaboration had produced for NIH's scientific research program.

Conclusion

In sum, the records and interviews conducted in this investigation raise serious questions of misconduct in connection with, and inadequate oversight and control over, human tissue samples in NIH intramural programs. It should be noted that the Committee staff found no evidence that Pfizer had any knowledge relating to the questionable conduct of Dr. Sunderland in connection with the April 1998 MTA and the subsequent shipments of samples. Members of the Subcommittee may wish to pursue these questions at the hearing with witnesses and/or other appropriate action.

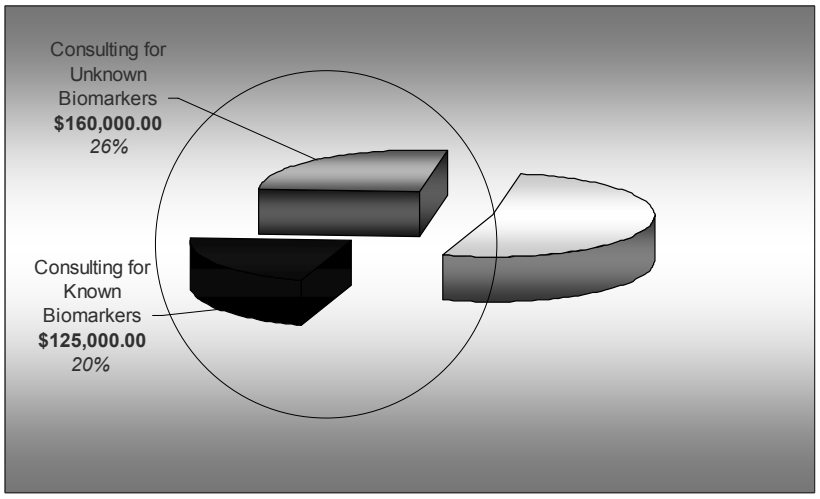
Pfizer Fees Paid to Dr. Trey Sunderland (1996-2004)

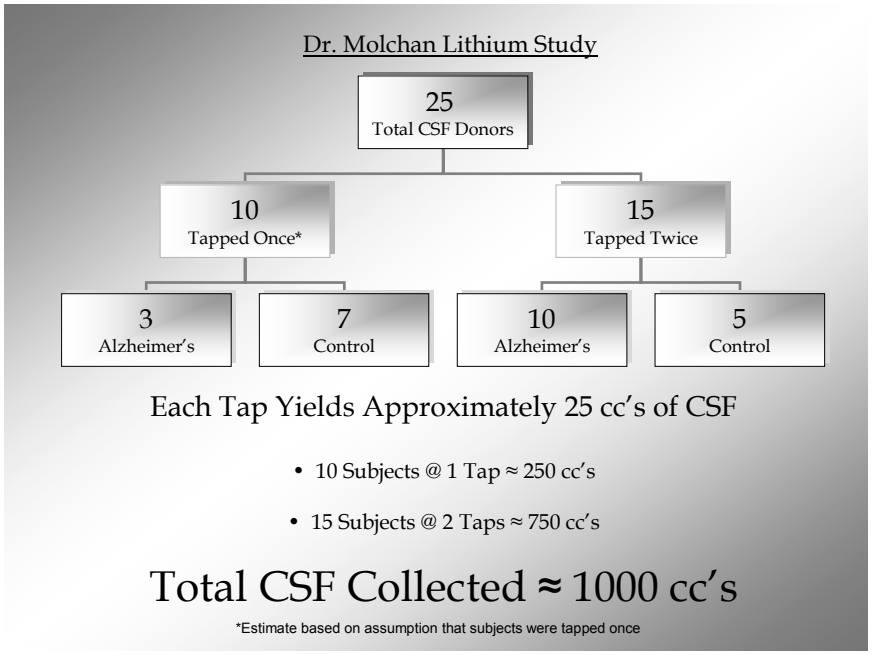


Total: Approximately $612,150.00

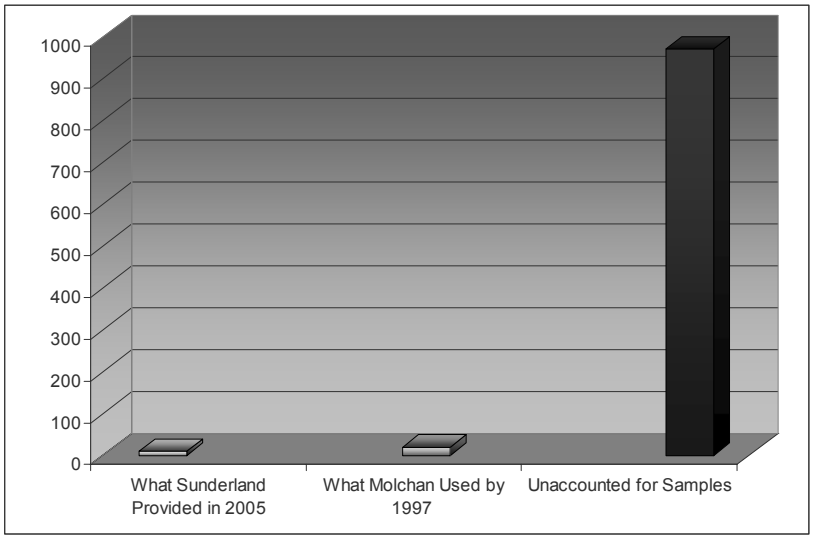
Fees Resulting from Human Samples Sent to Pfizer

[MAIN HEARING FOCUS]





Total Collected Spinal Fluid for Lithium Study = 1000 cc's



Dr. Sunderland's Shipments of Spinal Fluid to Pfizer

Shipment	Date	Number of Tubes	Study
1	6/24/1998	621	Unknown Biomarkers
2	2/9/1999	280	
3	2/22/1999	55	
4	3/24/1999	491	Unknown Biomarkers
5	5/5/1999	390	
6	2/3/2000	47	
7	4/3/2001	166	Unknown Biomarkers
8	12/1/2001	264	
9	8/19/2002	105	
10	8/11/2003	349	
11	Shipment 8 Transfer	207 Useable	
12	3/16/2004	570	

Total Tubes Shipped = 3245

Cost of collection to the NIH

- To Collect CSF
  - 538 Subjects at about $12,000 each

Total = $6,456,000.00

	DESCRIPTION		
	EXHIBIT		
1	MTA Cover letter	4/20/1998	
2	Material Transfer Agreement (MTA)	4/14/1998	1201
3	MTA with Desimo Signature	2/25/1999	
4	Amendment to MTA	10/6/2000	1206
5	Cover Letter to Draft MTA from Kathryn Smith to Sunderland	4/20/1998	
6	2D Gel Electrophoresis Consulting Agreement Cover Letter	5/29/1998	1215
7	Pfizer/Sunderland consulting agreement to study - biomarkers	5/1/1998	1211
8	Pfizer/Sunderland consulting agreement to study - biomarkers	11/1/1998	1219
9	Pfizer Summary and Justification of Sunderland Consultancy-Collaboration	11/27/2002	2107
10	Pfizer Justification for Putnam/Sunderland Consultancies	2/16/2004	2109
11	OMA Review of Putnam's Outside Activities at NIH	12/30/2004	
12	OMA Interview notification for Sunderland	8/19/2004	
13	OMA Interview with Dr. Sunderland - Version 1	8/19/2004	
14	OMA Interview with Dr. Sunderland - Version 2 (signed)	8/19/2004	
15	Pfizer e-mail re: minutes of Sunderland/NIH visit	3/5/1998	1240
16	E-mail from Boikess to Sunderland re: outside activities	6/18/2004	
17	E-mail from Boikess to Putnam re: filing activity forms	6/18/2004	
18	JAMA Article re: B-Amyloid & Tau Levels	4/23/2003	
19	Letter from the Committee to NIH	1/24/2006	
20	Letter from the Committee to NIH	6/20/2005	
21	Letter from Donnely to Putnam notifying of OMA review	12/7/2004	
22	Sample CSF Shipping Form and FedEx Receipt	2/2/2000	
23	E-mail from Kathy Smith to Pfizer people re: Sunderland	6/9/1998	1226
24	NIH Forms 1195 - Research protocol Review Applications	2002-2004	
25	Putnam draft memo on Pfizer samples	6/20/2005	
26	NIH doc on GPB/Pfizer Collaboration	Undated	
27	Letter from NIH Ethics Director to Putnam	5/10/2005	
28	Abbott Labs CRADA - 1989	6/27/1989	
29	Pfizer Patent	8/20/2001	
30	Patent Application	11/7/2002	
31	E-mail re: Kathy Smith phone call to Kathy Conn	3/24/1998	1236
32	Summary of OMA Report on Dr. Sunderland		
33	Letter from Putnam to OMA	12/7/2004	
34	Letter & Table of Services Provided by Sunderland to Pfizer and Fees	5/10/2006	
35	NIH Ethics Review Panel Findings - Dr. Sunderland	4/1/2005	
36	NIH Ethics Review Panel Findings - Karen Putnam	5/10/2005	
37	E-mail from Gemma Flamberg (NIH) to Alan Slobodin	6/1/2006	
38	"NIH Technology Transfer and You"		
39	List of Dates of Putnam Visits to Pfizer		2247
40	E-mail from Friedman to Pfizer people re: shipments	8/7/1998	1249
41	Stein, Mitchell & Mezines correspondence to NIH	8/31/2004	
42	Stein, Mitchell & Mezines correspondence to NIH	12/8/2004	

Tab 1

Central Research Division
Pfizer Inc
Eastern Point Road
Groton, CT 06340
Tel 860 441 5911 Fax 860 441 6491

Pfizer

Central Research

Research and Development Operations

April 20, 1998

SENT VIA FEDERAL EXPRESS

Trey Sunderland, M.D.
National Institute of Mental Health
Building 10, Room 3041
Bethesda, MD 20892

Dear Trey:

Enclosed for your records is one fully-signed copy of the MTA covering the Alzheimer's samples. I understand that David Friedman will be in touch to discuss transferring the samples in early May. Many thanks for all your help in finalizing the MTA. The draft consulting agreement will follow shortly, as we discussed, and I will be happy to talk with you when you get back. We are all very excited about getting this project underway.

Hope you had a wonderful time in China!

Sincerely,

Kathryn E. Smith, met

Kathryn E. Smith (formerly Monaghan)

:met
Enclosure

cc: D. L. Friedman

attached
PHS MTA Sunderland
4-14-98

bcc: B. M. Silber
S. A. Williams

Tab 2

20043500 file NIMH - Sec 4/20/98 Agmts/ List
cover letter attached (KLS)

PHS MATERIAL TRANSFER AGREEMENT

Signed 4-14-98

This Material Transfer Agreement ("MTA") has been adopted for use by the National Institutes of Health, the Food and Drug Administration and the Centers for Disease Control and Prevention, collectively referred to herein as the Public Health Service ("PHS") in all transfers of research material (Research Material) whether PHS is identified below as its Provider or Recipient.

Provider: Trey Sunderland, NIMH

Recipient: Pfizer Inc

1. Provider agrees to transfer to Recipient named below the following Research Material:

• Coded Clinical samples of cerebrospinal fluid (CSF) from over 250 subjects, including patients with Alzheimer's disease (AD), normal family members at risk for developing AD and elderly normal controls.

• Clinical information from the above patients/controls will include age, age of onset (for AD subjects), family history, duration of disease (for AD subjects) and severity of illness measures (for AD subjects).

2. THIS RESEARCH MATERIAL MAY NOT BE USED IN HUMAN SUBJECTS. The Research Material will only be used for research purposes by Recipient and Recipient's collaborator in the UK, for the research project described below, under suitable containment conditions. This Research Material will not be used for commercial purposes such as screening, production or sale, for which a commercialization license may be required. Recipient agrees to comply with all Federal rules and regulations applicable to the Research Project and the handling of the Research Material.

2(a). Are the Research Materials of human origin? __X_Yes ___No

2(b). If Yes in 2(a), were Research Materials collected according to 45 CFR Part 46, "Protection of Human Subjects?" _X__Yes (Please provide Assurance Number: M 1000)

3. This Research Material will be used by Recipient solely in connection with the following research project ("Research Project") described with specificity as follows (use an attachment page if necessary):

• Research to identify and validate protein markers associated with Alzheimers disease.

4. In all oral presentations or written publications concerning the Research Project, Recipient will acknowledge Provider's contribution of this Research Material unless requested otherwise. To the extent permitted by law, Recipient agrees to treat in confidence, for a period of three (3) years from the date of its disclosure, any of Provider's written information about this Research Material that is stamped "CONFIDENTIAL," except for information that was previously known to Recipient or that is or becomes publicly available or which is disclosed to Recipient without a confidentiality obligation. Any oral disclosures from Provider to Recipient shall be identified as being CONFIDENTIAL by notice delivered to Recipient within ten (10) days after the date of the

oral disclosure. Recipient may publish or otherwise publicly disclose the results of the Research Project, but if Provider has given CONFIDENTIAL information to Recipient such public disclosure may be made only after Provider has had thirty (30) days to review the proposed disclosure to determine if it includes any CONFIDENTIAL information, except when a shortened time period under court order or the Freedom of Information Act pertains.

5. This Research Material represents a significant investment on the part of Provider and is considered proprietary to Provider. Recipient therefore agrees to retain control over this Research Material and further agrees not to transfer the Research Material to other people not under her or his direct supervision without advance written approval of Provider. Provider reserves the right to distribute the Research Material to others and to use it for its own purposes. When the Research Project is completed or three (3) years have elapsed, whichever occurs first, the Research Material will be disposed of as directed by Provider.

6. This Research Material is provided as a service to the research community. IT IS BEING SUPPLIED TO RECIPIENT WITH NO WARRANTIES, EXPRESS OR IMPLIED, INCLUDING ANY WARRANTY OF MERCHANTABILITY OR FITNESS FOR A PARTICULAR PURPOSE. Provider makes no representations that the use of the Research Material will not infringe any patent or proprietary rights of third parties.

7. When Provider is the PHS: Recipient shall retain title to any patent or other intellectual property rights in inventions made by its employees in the course of the Research Project. Recipient agrees not to claim, infer, or imply Governmental endorsement of the Research Project, the institution or personnel conducting the Research Project or any resulting product(s). Unless prohibited by law from doing so, Recipient agrees to hold the United States Government harmless and to indemnify the Government for all liabilities, demands, damages, expenses and losses arising out of Recipient's use for any purpose of the Research Material.

8. When Recipient is the PHS: The PHS shall retain title to any patent or other intellectual property rights in inventions made by its employees in the course of the Research Project. The PHS is not authorized to promise rights in advance for inventions developed under this Agreement. Provider acquires no intellectual property rights under this MTA, but may apply for license rights to any patentable invention that might result from this Research Project. It is the intention of PHS that Provider not be liable to PHS for any claims or damages arising from PHS's use of the Research Material; however, no indemnification is provided or intended.

9. The undersigned Provider and Recipient expressly certify and affirm that the contents of any statements made herein are truthful and accurate.

10. This MTA shall be construed in accordance with Federal law as applied by the Federal courts in the District of Columbia.

11. Any additional terms:

Date: 4/14/98

Authorized Signature for Recipient and Title

Recipient's Mailing Address:

Pfizer Inc.
Central Research Division
Eastern Point Rd.
Groton, CT 06340

Provider's Investigator and Title: Trey Sunderland, M.D. Chief, Geriatric Psychiatry Branch, National Institute of Mental Health, Bethesda, Md.

Date: 4/8/98

Authorized Signature for Provider and Title

Provider's Mailing Address:

Trey Sunderland, M.D.
Geriatric Psychiatry Branch
10 Center Drive MSC 1275
Building 10/3N228
Bethesda, Md. 20892-1275

Tab 3

P-99-016 P-99 016

PHS MATERIAL TRANSFER AGREEMENT

This Material Transfer Agreement ("MTA") has been adopted for use by the National Institutes of Health, the Food and Drug Administration and the Centers for Disease Control and Prevention, collectively referred to herein as the Public Health Service ("PHS") in all transfers of research material (Research Material) whether PHS is identified below as its Provider or Recipient.

Provider: Trey Sunderland, NIMH

Recipient: Pfizer Inc

1. Provider agrees to transfer to Recipient named below the following Research Material:

• Coded Clinical samples of cerebrospinal fluid (CSF) from over 250 subjects, including patients with Alzheimer's disease (AD), normal family members at risk for developing AD and elderly normal controls.

• Clinical information from the above patients/controls will include age, age of onset (for AD subjects), family history, duration of disease (for AD subjects) and severity of illness measures (for AD subjects).

2. THIS RESEARCH MATERIAL MAY NOT BE USED IN HUMAN SUBJECTS. The Research Material will only be used for research purposes by Recipient and Recipient's collaborator in the UK, for the research project described below, under suitable containment conditions. This Research Material will not be used for commercial purposes such as screening, production or sale, for which a commercialization license may be required. Recipient agrees to comply with all Federal rules and regulations applicable to the Research Project and the handling of the Research Material.

2(a). Are the Research Materials of human origin? __X_Yes ___No

2(b). If Yes in 2(a), were Research Materials collected according to 45 CFR Part 46, "Protection of Human Subjects?" _X__Yes (Please provide Assurance Number: M 1000)

3. This Research Material will be used by Recipient solely in connection with the following research project ("Research Project") described with specificity as follows (use an attachment page if necessary):

• Research to identify and validate protein markers associated with Alzheimers disease.

4. In all oral presentations or written publications concerning the Research Project, Recipient will acknowledge Provider's contribution of this Research Material unless requested otherwise. To the extent permitted by law, Recipient agrees to treat in confidence, for a period of three (3) years from the date of its disclosure, any of Provider's written information about this Research Material that is stamped "CONFIDENTIAL," except for information that was previously known to Recipient or that is or becomes publicly available or which is disclosed to Recipient without a confidentiality obligation. Any oral disclosures from Provider to Recipient shall be identified as being CONFIDENTIAL by notice delivered to Recipient within ten (10) days after the date of the

oral disclosure. Recipient may publish or otherwise publicly disclose the results of the Research Project, but if Provider has given CONFIDENTIAL information to Recipient such public disclosure may be made only after Provider has had thirty (30) days to review the proposed disclosure to determine if it includes any CONFIDENTIAL information, except when a shortened time period under court order or the Freedom of Information Act pertains.

5. This Research Material represents a significant investment on the part of Provider and is considered proprietary to Provider. Recipient therefore agrees to retain control over this Research Material and further agrees not to transfer the Research Material to other people not under her or his direct supervision without advance written approval of Provider. Provider reserves the right to distribute the Research Material to others and to use it for its own purposes. When the Research Project is completed or three (3) years have elapsed, whichever occurs first, the Research Material will be disposed of as directed by Provider.

6. This Research Material is provided as a service to the research community. IT IS BEING SUPPLIED TO RECIPIENT WITH NO WARRANTIES, EXPRESS OR IMPLIED, INCLUDING ANY WARRANTY OF MERCHANTABILITY OR FITNESS FOR A PARTICULAR PURPOSE. Provider makes no representations that the use of the Research Material will not infringe any patent or proprietary rights of third parties.

7. When Provider is the PHS: Recipient shall retain title to any patent or other intellectual property rights in inventions made by its employees in the course of the Research Project. Recipient agrees not to claim, infer, or imply Governmental endorsement of the Research Project, the institution or personnel conducting the Research Project or any resulting product(s). Unless prohibited by law from doing so, Recipient agrees to hold the United States Government harmless and to indemnify the Government for all liabilities, demands, damages, expenses and losses arising out of Recipient's use for any purpose of the Research Material.

8. When Recipient is the PHS: The PHS shall retain title to any patent or other intellectual property rights in inventions made by its employees in the course of the Research Project. The PHS is not authorized to promise rights in advance for inventions developed under this Agreement. Provider acquires no intellectual property rights under this MTA, but may apply for license rights to any patentable invention that might result from this Research Project. It is the intention of PHS that Provider not be liable to PHS for any claims or damages arising from PHS's use of the Research Material; however, no indemnification is provided or intended.

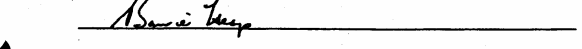
9. The undersigned Provider and Recipient expressly certify and affirm that the contents of any statements made herein are truthful and accurate.

10. This MTA shall be construed in accordance with Federal law as applied by the Federal courts in the District of Columbia.

11. Any additional terms:

Date: 4/14/98

Authorized Signature for Recipient and Title



Recipient's Mailing Address:

Pfizer Inc.
Central Research Division
Eastern Point Rd.
Groton, CT 06340

Provider's Investigator and Title: Trey Sunderland, M.D. Chief, Geriatric Psychiatry Branch, National Institute of Mental Health, Bethesda, Md.

Date: 4/8/98

Authorized Signature for Provider and Title

2-24-98

Provider's Mailing Address:

Trey Sunderland, M.D.
Geriatric Psychiatry Branch
10 Center Drive MSC 1275
Building 10/3N228
Bethesda, Md. 20892-1275

Tab 4

Worldwide Strategic & Operations Management
Pfizer Inc
Eastern Point Road
P.O. Box 8010
Groton, CT 06340-8010
Tel 860 441 1955 Fax 860 441 6491
Email barrie_hesp@groton.pfizer.com

FILE COPY

Global Research & Development

October 6, 2000

Barrie Hesp, D.Phil.
Vice President
External Technology PGRD

Trey Sunderland, MD
4718 Cumberland Avenue
Chevy Chase, MD 20815
USA

Dear Dr. Sunderland,

This letter will amend Article 1 of the PHS Material Transfer Agreement dated April 14, 1998 to include the following within Research Materials:

- Coded Clinical samples of serum from over 100 subjects, including patients with Alzheimer's disease (AD), normal family members at risk for developing AD and elderly normal controls.
- Coded Clinical samples of cerebrospinal fluid (CSF) from 75-150 additional subjects, including patients with Alzheimers disease (AD), normal family members at risk for developing AD and elderly normal controls.
- Clinical information from the above patients/controls will include age, age of onset (for AD subjects), family history, duration of disease (for AD subjects) and severity of illness measures (for AD subjects).

If you agree, please sign below and return an executed original of this agreement to us.

Very truly yours,

IN THE ABSENCE OF B. HESP

10/6/00
Date

for Barrie Hesp
Vice President, External Technology Investments

Agreed:

Trey Sunderland, MD

10/10/00
Date

CONFIDENTIAL
NOT FOR PUBLIC DISCLOSURE/FOIA EXEMPT

Tab 5

Central Research Division
Pfizer Inc
Eastern Point Road
Groton, CT 06340
Tel 860 441 5911 Fax 860 441 6491

Pfizer

Central Research

Research and Development Operations

April 20, 1998

Trey Sunderland, M.D.
4718 Cumberland Avenue
Chevy Chase, MD 20815

Dear Trey:

Attached is a draft consulting agreement. Let's talk when you get back.

All the best.

Sincerely,

Kathryn E. Smith (met)

Kathryn E. Smith (formerly Monaghan)

:met

Attachment

Tab 6

Central Research Division
Pfizer Inc
Eastern Point Road
Groton, CT 06340
Tel 860 441 5013 Fax 860 441 6491
Email kathryn_e_smith@groton.pfizer.com

Central Research

Kathryn E. Smith
Manager, External Technology
Research & Development Operations

May 29, 1998

SENT VIA FEDERAL EXPRESS

Trey Sunderland, M.D.
4718 Cumberland Avenue
Chevy Chase, MD 20815

Re: Consulting Agreement to Identify and Validate Protein Markers of Alzheimer's Disease using 2D Gel Electrophoresis technology

Dear Trey:

Enclosed please find two originals of the above-referenced agreement that have been signed on behalf of Pfizer. Please sign both originals and then return one fully-signed original to me.

If I can be of any further assistance, please do not hesitate to call.

Sincerely,

Kathryn E Smith met

Kathryn Smith (formerly Kathryn Monaghan)

:met

Enclosures

Tab 7

OGS agreement

(YES) just

FILE COPY

Central Research Division
Pfizer Inc
Eastern Point Road
Groton, CT 06340
Tel 860 441 1955 Fax 860 441 6491
Email: barrie_heap@groton.pfizer.com

Central Research

Barrie Heap, D.Phil.
Vice President
Technology Investments
Research and Development Operations

June 10, 1998

Trey Sunderland, M.D.
4718 Cumberland Avenue
Chevy Chase, MD 20815

20044223

Dear Dr. Sunderland:

As previously discussed, we would like to engage you as a consultant to assist us in our Alzheimer's Disease program.

The term of this Agreement will run for two (2) years from May 1, 1998. During this term, you agree to meet with us on mutually agreeable dates at mutually agreeable places. Members of our staff may also seek your advice from time to time on specific questions by telephone, e-mail or other media. Your compensation for the above term will be $25,000 per year and $2,500 per day for each one-day meeting. In addition, we will reimburse you for travel and lodging expenses in connection with visits to our laboratories, and for other expenses incurred by you at our request and on our behalf. You understand that all amounts due to you will be paid without deductions of any kind, and that you are responsible for payment of any applicable taxes.

During the course of your consultantship, you may receive confidential information from Pfizer. You agree not to use or disclose to third parties any such confidential information for as long as it remains unpublished except for information which is already known to you, is in the public domain or subsequently enters the public domain through no fault of yours. Pfizer agrees that it will not make public this agreement nor the terms associated with it.

If you become an inventor with respect to any of our developments, you agree, as is customary in agreements of this type, to assign to us any such invention conceived by you within the scope and arising from your consultation under this Agreement, without further compensation. This

assignment will include, at Pfizer's expense, the execution of such papers and documents necessary for Pfizer to obtain patents in the United States and abroad and your cooperation in obtaining such patents. Pfizer will pay expenses of preparing, filing and prosecution of any patent application.

You represent to Pfizer that you have full authority and right to enter into this Agreement, and that its terms will not conflict with any other agreement to which you are a party. In addition, you acknowledge that you are an independent contractor and, as such, are not entitled to any Pfizer employee benefits.

If this letter sets forth your understanding of our agreement, please sign one copy of this letter in the space provided and return it to us.

Sincerely,

Barrie Hesp

Agreed:

Trey Sunderland, M.D.

6/18/98
Date

cc: Pfizer Inc, Legal Division, Groton, CT 06340

Central Research Division
Pfizer Inc
Eastern Point Road
Groton, CT 06340
Tel 860 441 5013 Fax 860 441 6491
Email kathryn_e_smith@groton.pfizer.com

Pfizer

Central Research

Kathryn E. Smith
Manager, External Technology
Research & Development Operations

May 29, 1998

SENT VIA FEDERAL EXPRESS

Trey Sunderland, M.D.
4718 Cumberland Avenue
Chevy Chase, MD 20815

Re: Consulting Agreement to Identify and Validate Protein Markers of Alzheimer's Disease using 2D Gel Electrophoresis technology

Dear Trey:

Enclosed please find two originals of the above-referenced agreement that have been signed on behalf of Pfizer. Please sign both originals and then return one fully-signed original to me.

If I can be of any further assistance, please do not hesitate to call.

Sincerely,

Kathryn E Smith (met)

Kathryn Smith (formerly Kathryn Monaghan)

:met

Enclosures

Worldwide Strategic & Operations Management
Pfizer Inc
50 Pequot Avenue 6025-C5133
New London, CT 06320
Tel 860 732 8735 Fax 860 732 7028
Email alan_r_proctor@groton.pfizer.com

7/30/02

Global Research & Development

July 16th, 2002

Alan R. Proctor, Ph.D.
Vice President, PGRD
Head of Strategic Alliances

Trey Sunderland, MD
4718 Cumberland Avenue
Chevy Chase
MD 20815

Dear Dr Sunderland,

This letter will renew our consultancy agreement with you of May 1, 1988 (and extended for two years on October 1, 2000) in the area defined as "the study of biomarkers of neurological disease" on the same terms and conditions for a period of one (1) year beginning May 1, 2002. Your compensation for the above term will be $25,000 per annum.

If you agree, please sign below and return an executed original of this Agreement to us.

Sincerely,

Alan Proctor
Vice President
Strategic Alliances

Agreed:

Trey Sunderland, MD

7/30/02

Date

Worldwide Strategic & Operations Management
Pfizer Inc
Eastern Point Road
P.O. Box 8010
Groton, CT 06340-8010
Tel 860 441 1955 Fax 860 441 6491
Email barrie_hesp@groton.pfizer.com

FILE COP

Pfizer

Global Research & Development

September 18, 2000

Barrie Hesp, D.Phil.
Vice President
External Technology PGRD

Trey Sunderland, M.D.
4718 Cumberland Avenue
Chevy Chase, MD 20815

Dear Dr. Sunderland:

This letter will renew our consulting agreement with you of May 1, 1998 in the area of Alzheimer's Disease on the same terms and conditions for a period of two (2) years beginning May 1, 2000. Your compensation for the above term will be $25,000 per annum.

If you agree, please sign below and return an executed original of this agreement to us.

Sincerely,

Barrie Hesp, D. Phil.
Vice President
External Technology Investments

Agreed:

Trey Sunderland, M.D.

5.1.00

Date

Tab 8

FILE COPY

Consult. agmts/Inst (KES, BH

Central Research Division
Pfizer Inc
Eastern Point Road
Groton, CT 06340
Tel 860 441 4955 Fax 860 441 6491
Email: barrie_hop@groton.pfizer.com

Pfizer

Central Research

AGREEMENT

Barrie Hoop, D.Phil.
Vice President
Technology Investment-
Research and Development Operations

October 6, 1998

20047969
11-1-98

Trey Sunderland, M.D.
4718 Cumberland Avenue
Chevy Chase, MD 20815

Dear Dr. Sunderland:

As previously discussed, we would like to engage you as a consultant to assist us in our program to study known markers of Alzheimer's Disease.

The term of this Agreement will run for two (2) years from November 1, 1998. During this term, you agree to meet with us on mutually agreeable dates at mutually agreeable places. Members of our staff may also seek your advice from time to time on specific questions by telephone, e-mail or other media. Your compensation for the above term will be $25,000 per year. In addition, we will reimburse you for travel and lodging expenses in connection with visits to our laboratories, and for other expenses incurred by you at our request and on our behalf. You understand that all amounts due to you will be paid without deductions of any kind, and that you are responsible for payment of any applicable taxes.

During the course of your consultantship, you may receive confidential information from Pfizer. You agree not to use or disclose to third parties any such confidential information for as long as it remains unpublished except for information which is already known to you, is in the public domain or subsequently enters the public domain through no fault of yours. Pfizer agrees that it will not make public this agreement nor the terms associated with it.

If you become an inventor with respect to any of our developments, you agree, as is customary in agreements of this type, to assign to us any such invention conceived by you within the scope and arising from your

consultation under this Agreement, without further compensation. This assignment will include, at Pfizer's expense, the execution of such papers and documents necessary for Pfizer to obtain patents in the United States and abroad and your cooperation in obtaining such patents. Pfizer will pay expenses of preparing, filing and prosecution of any patent application.

You represent to Pfizer that you have full authority and right to enter into this Agreement, and that its terms will not conflict with any other agreement to which you are a party. In addition, you acknowledge that you are an independent contractor and, as such, are not entitled to any Pfizer employee benefits.

If this letter sets forth your understanding of our agreement, please sign one copy of this letter in the space provided and return it to us.

Sincerely,

Barrie Hesp

Agreed:

Trey Sunderland, M.D.

10/12/99
Date

cc: Pfizer Inc, Legal Division, Groton, CT 06340

Worldwide Strategic & Operations Management
Pfizer Inc
50 Pequot Avenue 6025-C5133
New London, CT 06320
Tel 860 732 3785 Fax 860 732 7028
Email alan_r_proctor@groton.pfizer.com

COR

Pfizer

Global Research & Development

Alan R. Proctor, Ph.D.
Vice President, PGRD
Head of Strategic Alliances

December 17th 2002

Trey Sunderland
4718 Cumberland Avenue
Chevy Chase
MD 20815

Dear Dr Sunderland,

This letter will renew our consultancy with you of November 1, 1998 (and extended for two years on November 1, 2000) in the area defined as "known markers of Alzheimer's Disease" on the same terms and conditions for a period of one (1) year beginning November 1, 2002. Your compensation for the above term will be $25,000.

If you agree, please sign below and return an executed original of this Agreement to us.

Sincerely,

PFIZER INC

Alan Proctor
Vice President
Strategic Alliances

Agreed:

Trey Sunderland, MD

1/14/03

Date

KES TRACK NO 19990226-04815

Worldwide Strategic & Operations Management
Pfizer Inc
50 Pequot Avenue
New London, CT 06320
Tel 860 732 3735

EFS

Global Research & Development

July 23, 2001

131149

Trey Sunderland, M.D.
4718 Cumberland Avenue
Chevy Chase, MD 20815

Dear Dr. Sunderland,

This letter will renew our consulting agreement with you of November 1, 1998 in the area of known markers of Alzheimer's Disease on the same terms and conditions for a period of two (2) years beginning November 1, 2000. Your compensation for the above term will be $25,000 per year.

If you agree, please sign below and return an executed original of this agreement to us.

Very truly yours,

PFIZER INC

By: _____
Alan R. Procter, Ph.D.

Agreed:

_____
Trey Sunderland, M.D.

7/31/01
Date

CONFIDENTIAL
NOT FOR PUBLIC DISCLOSURE/FOIA EXEMPT

Tab 9

Holly D. Soares
Senior Research Investigator
Clinical Biochemical Measurements

Global Research & Development
Pfizer Inc
Eastern Point Road
Groton, CT 06340
Tel 860 441 4100

Global Research & Development

To: Phil Vickers, Patrice Milos, Rob Sinclair, Kelly Longo, Trey Sunderland

From: Holly Soares

Date: November 27, 2002

Subject: Sunderland consultancy-collaboration

Summary:

Dr. Sunderland has been a long-time consultant with Pfizer and currently supplies expertise surrounding biomarker discovery efforts for Alzheimer's Disease. In addition, Dr. Sunderland provides Pfizer access to matched CSF/Plasma/Serum samples from AD patients and matched controls to enable biomarker validation. In the absence of an internal biobank, access to well-characterized clinical samples is an extremely valuable resource. The current proposal is requesting a 2 year consultancy and access to samples at a cost of $25,000/year (total cost $50K).

Impact:

- Use of a pre-existing historical clinical sample database would shorten the amount of time required to validate Level 2 (Pharmacodynamic) and Level 3 (Disease state) experimental biomarkers.
- Experimental biomarkers can be correlated a wide range of endpoints including ADAS-Cog; MMSE, CDR, GDS, NPI?, MRI brain volume and ApoE genotypes.
- Validation markers identified in AD/OGS collaboration.
- Validation of Plasma Abeta assay as Level 1 and Level 3 biomarker for internal Pfizer NDGN program.
- Validation of PhosphoTau assay as Level 1 and Level 3 biomarker for internal Pfizer NDGN program.

Background and Justification:

Alzheimer's disease is a chronic neurodegenerative disorder that strikes the elderly and is manifested by cognitive declines in learning and memory. It is estimated that over 4 million people suffer from Alzheimer's disease in the US with prevalence expected to quadruple in the next 50 years [1]. Current clinical trials rely upon subjective cognitive assessments that force clinical trial design towards large patient enrollment and prolonged duration. Thus, not only are current AD trials costly to run, but lengthy trial duration can detract from the patent life of candidates being developed. In addition, many of the compounds in the Pfizer pipeline are being targeted for disease modification. As a result, it is critical to be able to identify AD patients in the early stages of disease in order for these compounds to have the maximum desired efficacy. In theory, biomarkers

could alleviate the necessity for large patient enrollment by identifying those patients that are most likely to decline rapidly and by providing an independent quantitative measure to track progression. Furthermore, the ability to identify patients in the early stages of the disease ensures that the population most likely to benefit from treatment are identified.

Strategy and Detailed Budget:

The collaboration-consultancy will involve 3 different AD biomarker projects. The budget involves consultancy fees of $25,000 per year for two years. Total cost is $50,000.

These include:

1) Validation of Candidate Markers from the AD/OGS collaboration
    a. Study Design
    b. Deliverables
        i. Validated ICAT assay of top 30-50 MCI candidates.
2) Validation of CSF Abeta/total tau assays and correlation between CSF Abeta and plasma ABeta.
    a. Study Design
    b. Deliverables
        i. Validation of CSFABeta and Total tau as marker that can identify patients at risk of converting to AD.
3) Validation of PhosphoTau assay.
    a. Study Design
    b. Deliverables
        i. Validation of a PhosphoTau Assay
        ii. Validation of phosphotau as a marker that tracks with patients who have Alzheimer's disease and/or patients who are at risk of converting to AD.

Tab 10

Holly D. Soares
Senior Research Investigator
Clinical Biochemical Measurements

Global Research & Development
Pfizer Inc
Eastern Point Road
Groton, CT 06340
Tel 860 441 4100

Global Research & Development

To: Patrice Milos, Kelly Longo

From: Holly Soares

Date: February 16, 2004

Subject: Justification for Karen Putnam and Trey Sunderland consultancies-NIMH collaboration

Summary:

The CNS CBM lab has had a long-standing collaboration with Dr. Trey Sunderland and Karen Putnam surrounding biomarker development in Alzheimer's Disease. Dr. Sunderland and Karen Putnam were both granted consultancies in 2003. Both Trey Sunderland's and Karen Putnam's consultancy has expired and requires a 12 month renewal. Dr. Sunderland and Karen Putnam are currently providing CSF, plasma and serum samples from subjects with Alzheimer's Disease and from normal control subjects at risk of converting to AD. Dr. Sunderland is the lead clinician on the study and Karen Putnam is the database manager and lead statistician. In 2004, the goals of the collaboration are to determine whether AB42, AB40, Total Tau and pTau 231 are predictors of conversion to AD in an MCI population. In order to complete the projects, we will need to renew their consultancies until the end of 2004. The past consultancy was set at $25K per year for Dr. Sunderland and $15K/year for Karen Putnam. In the absence of an internal biobank, access to well-characterized clinical samples is an extremely valuable resource. Without these set of matched CSF-plasma samples, the lab will not be able to adequately validate use of Abeta, total Tau and PhosphoTau assays as Phase II outcome markers to support ongoing gamma secretase and LEADe clinical studies..

Impact:

- Validation of CSF Abeta, total tau and pTau assays predictors of conversion to AD in mild cognitively impaired population.

Budget:

The collaboration-consultancy will aid in the validation of Abeta and PhosphoTau assays in support of the secretase and Lipitor/Aricept programs run at PGRD. The budget involves consultancy fees of $40K per year.

Sincerely,
Holly Soares

Tab 11

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

National Institutes of Health
Bethesda, Maryland 20892
www.nih.gov

30 DEC 2004

Refer to: Case #2004-82-MH-63

TO: Ms. Chris Steyer
Acting Director, Office of Human Resources, OM

FROM: Director, Office of Management Assessment, OM

SUBJECT: Review of Outside Activities at NIH—Karen Putnam

PURPOSE. The Office of Management Assessment (OMA) has completed its review of discrepancies between records provided by the NIH and by Pfizer, Inc. to the U.S. House of Representatives, Committee on Energy and Commerce, Subcommittee on Oversight and Investigations, related to outside activities by Ms. Karen Putnam, Psychologist, Geriatric Psychiatry Branch (GPB), NIMH.

ALLEGATION. The Committee stated that Ms. Putnam received over $63,000 from Pfizer for consulting services and reimbursement for travel expenses. The Committee also asked that we analyze Ms. Putnam's long-distance working arrangement with NIMH.

FINDINGS. We found, and Ms. Putnam confirmed, that she did not submit any HHS forms 520, *Request for Approval of Outside Activity,* for her consulting work with Pfizer, violating NIH Policy Manual Chapter 2300-735-4, H., *Activities Which Require Prior Approval.* Ms. Putnam signed four one-year consulting agreements with Pfizer for 2001 through 2004. She said that she consulted for Pfizer on six occasions during that period but that she is no longer providing services to the company. Pfizer paid Ms. Putnam a total of $64,972.95 for her consulting services.

Ms. Putnam told OMA that she knew NIH employees needed approval to perform outside activities, but she did not believe that these requirements applied to her because of her grade level (GS-11), her part-time status, and because she would perform the work on her own time. She said that she discussed the issue with her supervisor, who told her that he did not believe she needed to file for approval. The supervisor told us that he does not recall whether he told Ms. Putnam that she should file any HHS forms 520. However, in an e-mail to Ms. Putnam, dated June 18, 2004, the NIMH Ethics Coordinator stated that the supervisor had called from abroad to say that he had advised Ms. Putnam that she did not have to file for prior approval.

We also found that Ms. Putnam was not on approved leave for four of the eight days that she consulted for Pfizer, violating NIH Policy Manual Chapter 2300-735-4, G.1.a.(4),

Use of Personal Time. Ms. Putnam did file a request to take annual leave for two days, November 19 and 20, 2001, but her supervisor denied the request. She told us that she was not notified of the denial. We learned, however, that both Ms. Putnam and her supervisor provided consulting services to Pfizer on these days, and neither was on approved leave. Ms. Putnam said that she did not take leave for the other activities because she made mistakes entering leave into the timekeeping system.

Ms. Putnam was not required to file any OGE forms 450, *Executive Branch Confidential Financial Disclosure Report,* or any SF forms 278, *Public Financial Disclosure Report,* during the period of the activities under review. According to NIH Policy Manual Chapter 2300-735-1, *Avoiding Conflicts of Interest*, she was not in a position that required filing, and the NIMH Deputy Ethics Counselor had not designated her as a filer.

We also analyzed Ms. Putnam's working arrangement with NIMH since moving to Cincinnati, Ohio, in August 1999. From the time of her move until January 2001, Ms. Putnam worked under a verbal telecommuting arrangement agreed to by NIMH. From January 2001 until January 2003, she had a formal IPA agreement with the University of Cincinnati. The NIMH Director, Scientific Director, and Executive Officer approved this agreement. On February 27, 2003, a formal telecommuting arrangement with NIMH was approved. Ms. Putnam told us that from August 1999 to the present, she has returned to NIMH GPB approximately once a month for three to four days. Prior to January 2001, Ms. Putnam paid her own travel expenses. From January 28, 2001, through September 1, 2004, NIMH paid $64,743 for Ms. Putnam's travel expenses.

CONCLUSION. We concluded that Ms. Putnam did not submit the required HHS forms 520 for her consulting work with Pfizer and was not on approved annual leave for four days while engaged in activities with Pfizer on July 24, 2001; November 19 and 20, 2001; and June 24, 2002.

RECOMMENDATION. We recommend you consult the NIH Table of Penalties and take appropriate administrative action.

COMMENTS ON OMA'S REVIEW AND OMA'S RESPONSE. In written comments on a draft of this report, Ms. Putnam stressed that she did request leave for two of the days she was on outside activities. However, her comments did not contain new or additional information that caused us to change our findings or recommendations. Ms. Putnam's comments are reprinted in their entirety in the attachment.

If you have any questions, please call Mr. Kevin Wetmore or me at (301) 496-1873.

Suzanne J. Servis

Attachment

cc: *w/attachment*
Mr. William Fitzsimmons, NIMH
Ms. Karen Putnam, NIMH

Tab 12

U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES
National Institutes of Health

OFFICE OF MANAGEMENT ASSESSMENT

INTERVIEW NOTIFICATION

For NIH Employee Management Reviews

Office of Management Assessment, Division of Program Integrity

We are here representing the National Institutes of Health, Office of Management Assessment, Division of Program Integrity (DPI). The DPI is conducting a review of an allegation of possible improper conduct. General authority for this review is set forth in section 402(b) of the Public Health Service Act, 42 U.S.C. 282(b).

Employee Cooperation: Your full cooperation in this review is requested. It is essential that your answers be truthful, complete, and accurate. False statements made to Government investigators may subject you to criminal prosecution under 18 U.S.C. 1001. Your responsibility to cooperate and to provide to the DPI statements or evidence related to this review is set forth in the HHS Standards of Conduct (Title 45, Code of Federal Regulations, Section 73.735.302[d]). Failure to cooperate may result in disciplinary action.

Confidentiality of Review: DPI is concerned that confidentiality of this matter be maintained by all involved parties. Further, we consider it essential for our effectiveness during the review. DPI requests that you share our commitment to preserving the confidentiality of these procedures.

I have read and understand the above explanation regarding the DPI review process and my obligation to cooperate.

Trey Sunderland
Signature of Interviewee

8/19/04
Date

NIH 2754-1 (12/94)

NIH-641-5

Tab 13

Interview with Dr. Trey Sunderland
August 19, 2004

Persons Present:
Dr. Trey Sunderland, Chief, Geriatric Psychiatry Branch, NIMH
Mr. Robert Muse, Attorney, Stein, Mitchell & Mezines
Mr. Arthur Hainer, Office of Management Assessment, NIH
Ms. Patricia Quast, Office of Management Assessment, NIH

Dr. Sunderland said that he began work at NIH in July 1982 and joined the Commissioned Corps in 1987. He became the Chief of the Geriatric Psychiatry Branch in the mid-1990s.

Dr. Sunderland said that he is aware that there are rules governing disclosure of financial interests and approval of official duties and outside activities and has taken the ethics course in the past. He said that he understands the concept, but may not have paid proper attention to it in the past. He said that he is now aware of how important these matters are and has either resubmitted or cancelled all his current outside activities. Dr. Sunderland told us that he understands the principles of 450s and 520s and felt that he had always disclosed his outside activities to his constituency—his colleagues, supervisors, and patients. He added that he made no attempt to hide his work with Pfizer, and has disclosed his outside activities in all of his lectures so that the audience knows his biases.

Dr. Sunderland told us that he felt that he had disclosed all of his activities with Pfizer. He recalled submitting the appropriate 520s for speeches and consultations with Pfizer, and that the majority of the activities were lectures, not consultations. He said that he remembered applying in September 1997 for approval of an infinite outside activity for a speaker's bureau for Pfizer. He said that he did not think that he needed to resubmit for ongoing activities, such as his private practice.

Dr. Sunderland said that, when he needed approval of an outside activity, he sent the 520 package to his secretary for processing. He added that he assumed that the activity was approved unless he heard otherwise and that he has never had an activity rejected. He added that he knew he shouldn't perform the activity until it was approved, but he hadn't been paying much attention to paperwork because he has been very busy with his science as well as with other administrative work, such as reviewing requests from patients, processing personnel papers, screening protocols, and writing papers. He said that he is also head of an Institutional Review Board. He said that he enjoyed the lack of emphasis on paperwork at NIH since it allowed him to put his time into other areas. He said that he had several secretaries in the last few years, including one that took him 2 years to fire. He said that the new secretary who replaced this one found piles of paperwork in the desk, left by the old secretary.

MH 64-4.1

Dr. Sunderland said that he does not know if he took annual leave for his outside activities because he doesn't track it, but that he works long, hard hours.

We asked Dr. Sunderland about the process for completing his 450. He told us that, when he looks at them now, he realized that they are inadequate. He said that he takes the form home, reviews his stock portfolio and his wife and children's financial interests, and fills out the first page of the form. He said that he uses his past form as the template to fill out the new form. He then signs the form and gives it to his secretary to fill in his outside activities, since he doesn't keep copies of his 520s. He said that, since he has already signed the form, he doesn't review it again after she completes it. He said that everything that is on his past 450s is accurate, but not complete.

Dr. Sunderland said that he did not keep copies of his 520s and does not have the 520s for any of the activities in question. He said that the dates from Pfizer do not represent the dates of his activities and that he is trying to find the dates now for us.

We asked Dr. Sunderland about his Material Transfer Agreements with Pfizer. He said that one is for a consulting arrangement with Pfizer Corporate and the other is with Pfizer Connecticut. He said that one is collaboration with David Friedman, who is a basic researcher for Pfizer. He said that he sent spinal fluid to Dr. Friedman, and that he has shared spinal fluid in over 30 other collaborations, including two with companies. He said that he thought an MTA would protect him from problems with his consulting arrangement with Pfizer. He said that one MTA had to do with proteomics and this project failed. The other MTA has been a successful project.

Dr. Sunderland said that his consulting work with Pfizer has to do with drug development and lectures. He said that he has avoided prescribing Pfizer drugs for his patients, although some may join his protocols already on Pfizer drugs.

Dr. Sunderland said that he has used a drug from Bristol Myers Squib in a clinical trial that was approved the end of 2001. He started work on the protocol in 1999 based on a drug used in Europe that he thought was a generic medication. However, he found out later, from the pharmacist, that this was not a generic medication and that only BMS supplied it. He added that they do not buy the drug direct from BMS. He said that the lectures he performed for BMS had nothing to do with this drug.

Dr. Sunderland said that he doesn't want his work to be biased and that he does not work with drug companies who try to insert their drugs into his work. He said that all his lectures are basically the same and that people want to hear the most recent scientific information without bias.

MH-64-4.2

We asked Dr. Sunderland about Karen Putnam's consulting work with Pfizer. He said that, in 2001, the proteomics project was in need of statistical help, and Pfizer asked if he knew anyone who could help. He said that he contacted Karen Putnam and John Bartko (ex-PHS officer, who had left the government) and discussed the consulting work with them and recommended them to Pfizer, who later contacted them.

When asked whether he had told Ms. Putnam that she needed to file a 520 for this activity, Dr. Sunderland said that he did not tell her to file or not to file—that it just wasn't an issue and did not come up. He said that he did not think that she needed to file because she was leaving NIH and because of her duties and grade level.

We asked Dr. Sunderland whether he knew if Ms. Putnam had taken leave for the time she was at Pfizer. He said that, although he is the approving official for Karen, he does not check to see if she has taken leave before he approves her time card because she is one of his hardest workers. Dr. Sunderland added that he looks for productivity, not hours, and only watches the leave records for people who do not work hard.

Dr. Sunderland said that he used to give the same types of lectures before Dr. Varmus allowed the scientists to personally keep honoraria, and that he contributed the honoraria to a pool.

Tab 14

Interview with Dr. Trey Sunderland
August 19, 2004

Persons Present:
Dr. Trey Sunderland, Chief, Geriatric Psychiatry Branch, NIMH
Mr. Robert Muse, Attorney, Stein, Mitchell & Mezines
Mr. Arthur Hainer, Office of Management Assessment, NIH
Ms. Patricia Quast, Office of Management Assessment, NIH

Dr. Sunderland said that he began work at NIH in July 1982 and joined the Commissioned Corps in 1987. He became the Chief of the Geriatric Psychiatry Branch in the mid-1990s.

Dr. Sunderland said that he is aware that there are rules governing disclosure of financial interests and approval of official duties and outside activities and has taken the ethics course in the past. He said that he understands the concept, but may not have paid proper attention to it in the past. He said that he is now aware of how important these matters are and has either resubmitted or cancelled all his current outside activities. Dr. Sunderland told us that he understands the principles of 450s and 520s and felt that he had always disclosed his outside activities to his constituency—his colleagues, supervisors, and patients. He added that he made no attempt to hide his work with Pfizer, and has disclosed his outside activities in all of his lectures so that the audience knows his potential biases.

Dr. Sunderland told us that he felt that he had disclosed all of his activities with Pfizer. He recalled submitting the appropriate 520s for speeches and consultations with Pfizer, and that the majority of the activities were lectures, not consultations. He said that he remembered applying in September 1997 for approval of consultation with Pfizer. Soon thereafter, he also requested an ongoing outside activity for a speaker's bureau for Pfizer. He said that he did not think that he needed to resubmit for ongoing activities, such as his private practice.

Dr. Sunderland said that when he needed approval of an outside activity, he gave the letter of invitation to his secretary for processing in the 520 package. He added that he assumed that the activity was approved unless he heard otherwise and that he cannot recall ever having an activity rejected. He added that he knew he shouldn't perform the activity until it was approved, but he hadn't been paying much attention to paperwork because he has been very busy with his science as well as with other administrative work, such as reviewing requests from patients, processing personnel papers, screening protocols, and writing papers. He said that he was also head of the NIMH Institutional Review Board during much of the period in question with the burden of tremendous additional administrative paperwork. He said that he enjoyed the lack of emphasis on

paperwork at NIH since it allowed him to put his time into other areas. He said that he had several secretaries in the last few years, including one that took him 2 years to transfer her into another position because of administrative weaknesses. He said that the new secretary who replaced this one found piles of paperwork under the desk, left by the old secretary.

Dr. Sunderland said that he does not know if he took annual leave for his outside activities because he doesn't track it, but that he works long, hard hours, like many of his colleagues.

We asked Dr. Sunderland about the process for completing his 450. He told us that, when he looks at them now, he realized that they are inadequate. He said that he takes the form home, reviews his stock portfolio and his wife's and children's financial interests, and fills out the first page of the form, including the signature. He said that he uses his past form as the template to fill out the new form. He then signs the form and gives it to his secretary to help gather his outside activities, since he doesn't keep copies of his 520s. He said that, since he has already signed the form, he doesn't review it again after she helps complete it. He said that everything that is on his past 450s is accurate, but not complete.

Dr. Sunderland said that he did not keep copies of his 520s and does not have the 520s for most of the activities in question. He said that the dates from Pfizer do not represent the dates of his activities and that he is trying to find the dates now for us.

We asked Dr. Sunderland about his Material Transfer Agreement with Pfizer. He said that he had a consulting arrangement with Pfizer Corporate and the MTA with Pfizer researchers in Connecticut. He said that the scientific collaboration was initiated by David Friedman, who was a basic researcher for Pfizer. He said that he sent spinal fluid to Dr. Friedman, and that he has shared spinal fluid in more than 30 other collaborations, including two with companies over the last 20 years and that this was his only MTA. He said that the scientific collaboration itself would not have required visits to Pfizer, as this was an exchange of material for analytical data, like many of his other collaborations. He said that he thought an MTA would protect him and Pfizer from issues of conflict because of his consulting arrangement with Pfizer. He said that part of the MTA had to do with proteomics and this project failed. The other part of the MTA has been a successful project.

Dr. Sunderland said that his consulting work with Pfizer has to do with drug development and lectures. He said that he has avoided studying Pfizer drugs in any of his NIH research protocols, although some patients may join his protocols already on Pfizer drugs clinically.

Dr. Sunderland said that he has studied a drug from Bristol Myers Squib in a clinical trial that was approved the end of 2001. He started work on the protocol

in 1999 based on a drug used in Europe that he thought was a generic medication. However, he found out only this August, from the pharmacist, that this was not a generic medication and that only BMS supplied it. He added that they do not buy the drug direct from BMS and that he has not had contact with BMS about this protocol. He said that the lectures he performed for BMS had nothing to do with this drug.

Dr. Sunderland said that he doesn't want his perspective to be biased and that he does not work with drug companies who try to insert their slides into his lectures. He said that all his lectures offer basically the same perspective no matter who is the sponsor and that people want to hear the most recent scientific information without bias.

We asked Dr. Sunderland about Karen Putnam's consulting work with Pfizer. He said that, in 2001, the proteomics project was in need of statistical help, and Pfizer asked if he knew anyone who could help. He said that he contacted Karen Putnam and John Bartko (ex-PHS officer, who had left the government) and discussed the consulting work with them and recommended them to Pfizer, who later contacted them.

When asked whether he had told Ms. Putnam that she needed to file a 520 for this activity, Dr. Sunderland said that he does not recall if he told her to file or not to file. He said that he does not think that she needed to file because she was a part-time employee on an IPA at the time and because her duties did not overlap with any decisions regarding drug or protocol development.

We asked Dr. Sunderland whether he knew if Ms. Putnam had taken leave for the time she was at Pfizer. He said that, although he is the approving official for Karen, he does not check to see if she has taken leave before he approves her time card, but he would probably have mentioned the need to take leave for the outside consulting work. Dr. Sunderland added that he looks for productivity, not hours in all his employees and only watches the leave records for people who do not work hard.

Dr. Sunderland said that he used to give the same types of lectures before Dr. Varmus allowed the scientists to personally keep honoraria, and that he contributed the honoraria to a government pool.

( ) These notes accurately summarize the interview.

(X) These notes, with indicated changes, accurately summarize the interview.

Signature 8/31/04 Date

1 of 6

Tab 15

cc:Mail for: kathryn e monaghan

Subject:

From: Julie A Olson at CR_GROTON_NONCLIN10 3/5/98 11:49 AM
To: B Michael Silber at CR_GROTON_NONCLIN25
To: Ian H Williams at CR_GROTON_NONCLINICAL02
To: Jeffrey A Stritar at CR_GROTON_CLIN05
cc: Stephen A. Williams at CR_GROTON_CLIN01
cc: Edward F Pun at CR_GROTON_CLIN02
cc: David L Friedman at CR_GROTON_NONCLIN15
To: Kathryn E Monaghan

Re MTA

I'm pleased that this is working out well, both on the scientist to scientist side and on the tech transfer side. We do not need to have the MTA signed prior to CMC on March 12. Julie

Subject: Minutes of Sunderland/NIH Visit - Impact on OGS Deal/CMC
From: B Michael Silber at CR_GROTON_NONCLIN25
Date: 2/24/98 9:33 AM

Ian, Jeff, Kathy,

Steve Williams, Ed Pun , David Friedman and I visited with Trey Sunderland at the NIH on Friday, February 20 regarding the serum and CSF samples and linked clinical information on the AD patients in his cohort at NIH.

We were impressed with Trey, his patient cohort and the care that he clearly has shown and continues to show in AD research. We were in agreement that he likely has the best cohort of patients, patient samples and clinical information of anyone or any institution. The number of AD patients is large and the SAS data set was briefly reviwed. In order for Ed Pun to have more of an opportunity to carefully review the SAS database, Trey promised to send copies of anonymyzed patient information within about 1 week (he will be out most of this week). David and I will follow up with Trey to ensure the materials are sent to Ed Pun as soon as possible.

Assuming Ed's review of the SAS based database and information collected continues to look positive, we are bullish about going forward. In discussions regarding Pfizer's needs and Sunderland's needs, Trey indicated that he was very happy with an MTA arrangement plus consulting that Kathy has been discussing. Trey was also very interested in publication. He wanted to make sure that Pfizer was also interested in publication in a reasonable time frame and that he wanted to make sure that authorship would be based on scientific and intellectual contributions. We indicated agreement on both matters. We emphasized that publication could be considered after appropriate patent applications or other considerations had been addressed. He was very pleased with this.

Given the approaching March 12 CMC on the OGS deal, the last major hurdle, assuming Ed Pun's review of SAS outputs next week goes smoothly, is to complete the MTA with Sunderland/NIH regarding the transfer of samples and clinical information. He knows there is a third party that will be involved in applying technology. He was very interested in having the opportunity to visit this third party to see for himself that they had the tools and ability to do what we are intending to do. We told him that this would not be a problem. This could be arranged. Trey was also very

interested in this being a truly collaborative project where he is aware of the experiments being done and data is shared with him. We indicated that this was our desire and plan as well. He was very pleased with what he heard and the type of collaboration that had been laid out.

I am assuming that we need to have the MTA completed and signed with NIH prior to going to the CMC so that we can ensure that we know which clinical samples/linked information will be used in the OGS deal. Call, Steve, Ed, David or me if you have any questions regarding our visit.

Thanks,

Michael

CONFIDENTIAL
NOT FOR PUBLIC DISCLOSURE/FOIA EXEMPT

Tab 16

Boikess, Olga (NIH/NIMH)

m:	Boikess, Olga (NIH/NIMH)
t:	Friday, June 18, 2004 3:47 PM
o:	Sunderland, Trey (NIH/NIMH)
Cc:	Fitzsimmons, William (NIH/NIMH); Wexler, Pamela (NIH/NIMH)
Subject:	outside activity - Congressional inquiries

There is a hearing on Tuesday so we would appreciate any help you can give us.

As I explained, Congress asked various drug companies if they had had any consulting arrangements with NIH employees.

This is what Congress tells NIH that Pfizer has reported: "Dr. Pearson Sunderland, III (Trey) listed by Pfizer as having various consulting agreements with it from 1998 to the present, receiving over $517,000 in fees and expense reimbursements. NIH did not identify any agreements for this employee with Pfizer. We do not have paperwork from NIH on these agreements."

Except for the request to attend the Pfizer meeting in March 2004, this office has no record of outside activity requests from you involving Pfizer. Your 450 reports do not report any income from Pfizer. There is a record of an MTA agreement with Pfizer signed in 4/98. Could the payments have related to that?

Can you help us, please? What is the explanation? thanks Olga 301-443-3877

Tab 17

Boikess, Olga (NIH/NIMH)

m: Putnam, Karen T. (NIH/NIMH)
t: Friday, June 18, 2004 2:04 PM
To: Boikess, Olga (NIH/NIMH)
Cc: Sunderland, Trey (NIH/NIMH)
Subject: RE:

Dear Ms. Boikess,

Thank you for your response. What you have written is true and I understand what you have told me. I will certainly plan to discuss this further with you and Dr. Sunderland upon his return.

Sincerely,
Karen Putnam

From: Boikess, Olga (NIH/NIMH)
Sent: Friday, June 18, 2004 1:44 PM
To: Putnam, Karen T. (NIH/NIMH)
Cc: Sunderland, Trey (NIH/NIMH)
Subject:

Dr. Sunderland called me from abroad. He is very concerned. He tells me that he advised you that you did not have to file for permission to have an outside activity with Pfizer. I have told NIH that.

Of course, from now on, you may not continue to perform an activity with Pfizer, or any other similar activity, without prior approval. As soon as Dr. Sunderland returns, we can discuss this together. Then, if you want to continue to do work for Pfizer, you can apply for approval. feel free to call me if you want to dicuss this. Olga Boikess

MH-63-105-F-15

Tab 18

ORIGINAL CONTRIBUTION

Decreased β-Amyloid$_{1-42}$ and Increased Tau Levels in Cerebrospinal Fluid of Patients With Alzheimer Disease

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Nadeem Mirza, MD
Karen T. Putnam
David L. Friedman, PhD
Lida H. Kimmel, MS
Judy Bergeson, MA
Guy J. Manetti
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Brian Tang
John J. Bartko, PhD
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Context Alzheimer disease (AD) is characterized by pathological results at autopsy of amyloid plaques and tau-associated neurofibrillary tangles, but the clinical diagnosis of AD is determined on the basis of medical history, cognitive symptoms, and exclusionary criteria. The search for antemortem biomarkers is intense and has focused on cerebrospinal fluid (CSF) β-amyloid$_{1-42}$ and tau proteins.

Objectives To compare CSF β-amyloid and tau levels in a new population of AD patients and controls. To perform a meta-analysis of studies of CSF β-amyloid and tau levels in AD patients and controls.

Design Cross-sectional study of the comparison of baseline CSF β-amyloid$_{1-42}$ and tau levels in AD patients and controls. Meta-analysis involved 17 studies of CSF β-amyloid and 34 studies of CSF tau.

Setting Clinical research unit of the National Institute of Mental Health, Bethesda, Md.

Patients The Geriatric Psychiatry Branch evaluated AD patients as inpatients at the National Institutes of Health Clinical Center between May 1985 and January 2001. A total of 203 patients participated in this study (131 with AD and 72 controls). None had other serious illnesses, and 31 of 131 AD cases had AD confirmed at autopsy. Meta-analysis provided an additional 3133 AD patients and 1481 controls.

Main Outcome Measures Levels of CSF β-amyloid$_{1-42}$ were measured by a sandwich enzyme-linked immunoabsorbent assay with a polyclonal capture antibody and a monoclonal detection antibody. Levels of CSF tau were measured with a standard commercial immunoassay.

Results Levels of CSF β-amyloid$_{1-42}$ were significantly lower in the AD patients vs controls (mean [SD], 183 [121] pg/mL vs 491 [245] pg/mL; $P<.001$). Levels of CSF tau were significantly higher in AD patients (mean [SD], 587 [365] pg/mL vs 244 [156] pg/mL; $P<.001$). The cutpoints of 444 pg/mL for CSF β-amyloid$_{1-42}$ and 195 pg/mL for CSF tau gave a sensitivity and specificity of 92% and 89%, respectively, to distinguish AD patients from controls, which is comparable with rates with clinical diagnosis. Meta-analyses of studies comparing CSF β-amyloid and tau levels in AD participants and controls confirmed an overall difference between levels in these 2 groups.

Conclusions Alzheimer disease is associated with a significant decrease in CSF β-amyloid$_{1-42}$ levels along with an increase in CSF tau levels. These findings suggest that the 2 measures are biological markers of AD pathophysiology. While these CSF measures may have a potential clinical utility as biomarkers of disease, the preliminary and retrospective nature of the findings, the absence of assay standardization, and the lack of comparison patient populations must be addressed in future studies testing the usefulness of these CSF measures for predictive, diagnostic, or treatment evaluation purposes.

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www.jama.com

WHILE THE EXACT BIOLOGICAL cascade associated with Alzheimer disease (AD) is only partially understood, many potential biomarkers of this disease process are known.[1] Two of the most obvious candidates are β-amyloid$_{1-42}$ and tau proteins, as they are intimately related to the pathognomonic features of amyloid plaques and neurofibrillary tangles in the AD brain.[2,3] Multiple previous studies have reported ~~decreases in cerebrospinal fluid~~ (CSF) measures of β-amyloid.[4-7] Similarly, CSF measures of ~~tau have routinely showed considerable elevations of this peptide~~ in AD cases worldwide.[7-12] Some authors have reported that these 2 measures alone can accurately differentiate clinically diagnosed AD cases from controls ~~more than 85% of the time~~.[7,13]

Studies of CSF in AD patients have used widely varying methods and nomenclature for assessing and describ-

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ing CSF β-amyloid$_{1-42}$.[4,6,7,14,15] Furthermore, while the majority of studies report decreases in CSF β-amyloid levels in AD patients, some studies show no significant change or even a slight increase in CSF β-amyloid levels in AD patients when compared with controls.[16,17] Finally, the majority of CSF β-amyloid reports include a paucity of participants. We assessed CSF β-amyloid and tau levels in the largest cohort of AD patients and controls evaluated to date, to our knowledge. In addition, we performed a meta-analysis of CSF β-amyloid$_{1-42}$ and tau to help clarify whether consistent trends emerged.

METHODS

Participants

A total of 208 participants (136 with AD and 72 controls) were evaluated as part of an ongoing study of AD. (Five patients were excluded after autopsy showed they did not have AD. See "Autopsy" section.) Patients with AD were referred by their primary physician, and controls were self-referred, in response to local advertisements, as unpaid volunteers. Participants signed informed consent documents for this prospective study after approval of the National Institute of Mental Health institutional review board (protocols 82-M-123 and 95-M-96). For AD patients (n=136), signed informed consent was obtained from the patient and from the individual's durable power of attorney for research decisions, as previously described.[18,19] All AD patients were given both written and verbal explanations of the study procedures involved, and repeated assent was required before any individual procedure could proceed. For the control participants, written informed consent was obtained in a routine fashion.

Clinical Evaluation

The Geriatric Psychiatry Branch evaluated AD patients as inpatients at the National Institutes of Health Clinical Center between May 1985 and January 2001. Evaluation included thorough medical screenings, neurocognitive profiling, magnetic resonance imaging scan, lumbar puncture for CSF examination, and behavioral observations for 1 to 2 weeks. Individuals were participating in a longitudinal study of biological changes that occur over time in AD (protocols 82-M-123 and 95-M-96). Medical evaluations for all participants included a physical examination, a routine electrocardiogram, and blood tests (eg, venereal disease research laboratory test for syphilis, complete blood cell count, vitamin B_{12} levels, and thyroid function tests) to eliminate other known contributors to memory impairment. Routine computed tomography scans or magnetic resonance imaging scans (1.5 tesla) also were performed to exclude the possibility of overt cerebrovascular disease. Controls underwent medical evaluations to exclude serious medical illnesses (eg, type 1 diabetes mellitus, significant hypertension, or cardiovascular disease).

Clinical Assessment

Trained inpatient staff administered to all participants several global clinical rating instruments, including the Clinical Dementia Rating (CDR),[20] Global Deterioration Scale (GDS),[21] and the Mini-Mental State Examination (MMSE).[22] These well-established rating instruments were given within 1 month of the lumbar punctures. Patients with AD were diagnosed according to *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition*, and NINCDS-ADRDA criteria.[23,24]

Lumbar Puncture

Lumbar punctures were performed at the start of the morning. Participants were inpatients at the National Institutes of Health Clinical Center and were kept at bedrest and had nothing by mouth until the procedure was completed. While the patient was in the lateral decubitus or sitting position, lumbar punctures were performed with a 20- or 22-gauge needle after application of local anesthesia with 1% to 2% lidocaine. Headache rates following lumbar punctures were less than 10% (ranging from mild discomfort to severe headaches requiring follow-up care with a blood patch). Approximately 30 mL of CSF was withdrawn during the lumbar puncture; the CSF was aliquoted into individual polypropylene tubes without preservative and frozen at the bedside on dry ice within minutes of withdrawal. Samples were then transferred to −70°C freezers. The low-temperature freezers are monitored daily for temperature control, and they have auxiliary liquid carbon dioxide backup in case of mechanical or electrical failures.

CSF Assays

Assays were performed on the CSF samples from AD patients that had been stored undisturbed at −70°C for variable lengths of time, ranging from less than 6 months to longer than 15 years. Since the time samples were stored in the freezer before CSF assay (shelf life) differed significantly by diagnostic category (mean [SD] for controls, 3.1 [2.9] years vs for AD patients, 7.1 [3.4] years; $P<.001$), we tested whether shelf life was associated with CSF β-amyloid$_{1-42}$ or tau levels. Within the control group, neither CSF β-amyloid$_{1-42}$ nor tau levels were significantly correlated with duration of shelf life ($r=-0.03$, $P=.78$ and $r=0.02$, $P=.81$, respectively). Similarly, neither CSF β-amyloid$_{1-42}$ nor tau levels were significantly associated with duration of shelf life in the AD group ($r=-0.07$, $P=.33$ and $r=0.02$, $P=.79$, respectively).

CSF β-Amyloid$_{1-42}$ Levels. β-Amyloid$_{1-42}$ was measured with a 1-step sandwich enzyme-linked immunoabsorbent assay (IGEN International Inc, Gaithersburg, Md) using a polyclonal antibody specific for β-amyloid$_{1-42}$ used as the capture antibody and a monoclonal antibody, 4G8, used as the detection antibody. This assay is designed specifically to measure the human β-amyloid 1-42 peptide in CSF in a 10× excess background of 1-40. The monoclonal antibody (catalog No. 4G8 240-10; Senetek, Napa, Calif) was supplied in the form of purified IgG at 1 mg/mL and ruthinylated at 7:1 ratio. The β-amyloid polyclonal antisera (cata-

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log No. 44-344; QCB Division of BioSource International, Hopkinton, Mass) was supplied as 0.530 mg/mL and biotinylated at a 20:1 ratio. β-Amyloid peptide (catalog No. 03-111 [1-42] and catalog No. 03-136[1-40]; QCB) was supplied as 1 mg and as trifluoroacetate salt. Solubilization was performed in 1 mg/mL of dimethylsulfoxide and snap frozen on dry ice. Samples of CSF (200 µL) or standards (200 µL) were added to 50 µL of antibody (4 µg/mL of monoclonal antibody 4G8 and 3 µg/mL of polyclonal antibody) and 25 µL of streptavidin M-280 paramagnetic beads (IGEN International Inc) at 600 µg/mL, which was prepared in phosphate buffered saline with 15% bovine serum albumin. This mixture was incubated at room temperature for 3 hours with shaking followed by the addition of 300 µL of phosphate buffered saline at the end of the incubation period.

The immune complexes were quantitated by measurement of electrochemiluminescent signal using an ORIGEN 1.5 Analyzer (IGEN International Inc) with 5 standard concentrations from 125 to 2000 pg/mL. The intra-assay variability was assessed by calculating the percent coefficient variation for replicates of the individual samples on the same assay and then averaging those values for each assay. Using a standard curve, the inter-assay variability was determined by calculating the percent coefficient variation for the quality control samples across all of the assays. Intra-assay and inter-assay variability measures were 3.5% and 5.2%, respectively.

CSF Tau Protein Levels. Tau was measured using a commercial enzyme immunoassay (Innotest Inc, Ghent, Belgium). In this assay, the wells of polystyrene microtiter plates were coated with the solid phase anti–human tau monoclonal antibody (AT120). The test samples were incubated in these wells along with 2 separate biotinylated tau monoclonal antibodies (H57 and BT2) that recognize different tau epitopes. Samples were rinsed with an assay buffer and then incubated with peroxidase-labeled streptavidin. Samples were then incubated with tetramethylbenzidine and 0.006% hydrogen peroxide per manufacturer's instructions. The reaction was stopped with diluted sulfuric acid and optical density measurements read using a Molecular Devices Spectramax Plus plate reader. Intra-assay and inter-assay variability measures were 5.6% and 8.1%, respectively.

Autopsy. The original clinical population consisted of 136 patients with "probable" AD. Of those patients, 36 have since died and undergone autopsy. The diagnosis of AD was confirmed in 31 of 36 patients (86% accuracy) according to standard neuropathologic criteria[25,26] without knowledge of CSF data. Autopsy results revealed that 5 cases of clinical AD were found to have other neuropathological diagnoses: 2 with Lewy body dementia, 2 with cerebrovascular dementia, and 1 with thalamic dementia. These cases were excluded from the dataset for the CSF analysis. The final AD group (n = 131) consists of 100 patients with "probable" AD who are still alive and 31 patients with autopsy-proven AD.

Statistical Analysis

Parametric comparisons between the AD and control groups were performed using unpaired *t* tests. Satterthwaite adjusted *t* tests and degrees of freedom are reported when the group variances were unequal. Pearson correlation coefficient was used for exploratory correlations within groups. When our key outcome measures (ie, CSF β-amyloid$_{1-42}$ and tau) were significantly correlated with the baseline variables ($P<.05$), factorial designs were applied to the data with sex and age as grouping variables.[27] Data are expressed as mean (SD) unless otherwise specified. All analyses were performed using the software packages of SAS version 8.02 (SAS Institute, Cary, NC), CART version 3.6 (Salford Systems, San Diego, Calif), and NCSS 2001 (Kaysville, Utah).

A classification and regression tree (CART) is a nonparametric, binary decision tree method of analysis (an "if-then" scenario) similar to the diagnostic decision trees used in differential diagnosis in medicine,[28] especially when looking for relationships between a small number of variables.[29] The CART approach allows for variables to be tested simultaneously for diagnostic classification without relying on classical statistical assumptions, such as the normality of the data and homogeneity of variance. CART also was used to estimate objective bivariate cutpoints for the CSF variables to determine maximal sensitivity and specificity associated with the clinical diagnosis of AD. In this analysis, the lead variable was CSF β-amyloid$_{1-42}$ followed by CSF tau.

A meta-analysis of CSF β-amyloid$_{1-42}$ comparisons in AD and control participants was performed by calculating and combining the effect sizes and *t* test scores across 17 CSF studies.[30] These studies were chosen from 188 articles that resulted from PubMed and MEDLINE literature searches from August 1989 to March 2003 using key words *Alzheimer's* and *CSF* and *beta-amyloid*, or *amyloid beta* in titles and abstracts. Studies were sorted according to relevance and were excluded if they were not in the English language, did not provide data for controls, did not provide diagnostic criteria, or failed to distinguish total CSF β-amyloid from its components (40 and 42 residue chains). Studies with fewer than 25 total participants or those that did not report the SD of the mean CSF β-amyloid level also were excluded. If identical or overlapping population samples were used in 2 separate articles, a judgment was made to include the more complete article in the meta-analysis. After application of these criteria, a total of 17 studies were included in the meta-analysis. In this meta-analysis, studies were weighted according to sample size.[27] Effect size was calculated by dividing the difference of the means for the outcome variable by the pooled SD.[31]

A meta-analysis using the same procedures also was performed for articles reporting CSF tau levels across the same time period as CSF β-amyloid$_{1-42}$ levels. Again, articles were excluded from further consideration if they included previously reported data, did not include control participants, had poorly de-

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scribed methods, included mixed diagnostic populations, had missing SDs for mean CSF tau levels, or had fewer than 25 participants. The initial list of 200 articles was reduced to a final count of 34 relevant studies for the meta-analysis focusing on CSF tau levels.

Because the underlying units of measurement varied from study to study, all units were converted to picograms per milliliter using a commonly available calculator program (http://molbiol.ru/eng/scripts/01_04.html). The overall effect size and t test with the associated P value were calculated for this meta-analysis.[32] The t tests were calculated with unequal variances using the Satterthwaite adjusted degrees of freedom rounded to the nearest integer.

RESULTS

Baseline and Global Measures

The 131 AD participants (mean [SD] age, 68.1 [9.1] years; range, 44-88 years) had a mean (SD) age of dementia onset of 64.4 (9.4) years and duration of illness of 3.6 (2.4) years. The AD participants were mildly to moderately impaired with mean (SD) MMSE scores of 19.7 (6.7). The control participants (n=72; mean [SD] age, 59.4 [8.5] years; range, 45-86 years) were significantly younger and more educated than the AD patients (TABLE 1).

CSF Measures of β-Amyloid$_{1-42}$ and Tau

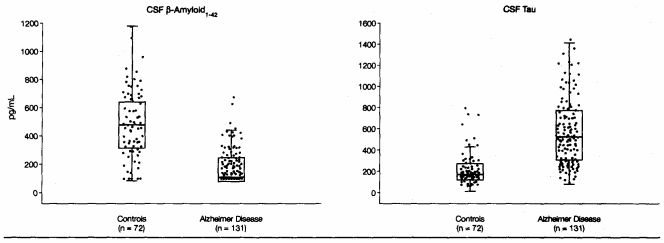
Mean (SD) CSF β-amyloid$_{1-42}$ were significantly lower in the AD patients compared with the controls (183 [121] pg/mL vs 491 [245] pg/mL; $P < .001$). Despite the statistically significant differences between groups, the data showed considerable variance, resulting in significant overlap between groups (FIGURE 1). Marked differences in mean CSF tau levels between AD patients and controls also were observed (587 [365] pg/mL vs 224 [156] pg/mL; $P < .001$). For CSF tau, tau concentration was significantly associated with age of controls ($r=0.43$, $P<.001$) but not age of AD patients ($r=0.012$, $P=.90$). Conversely, there was a significant sex effect with mean (SD) CSF tau in the AD patients (men, 506 [258] pg/mL vs women, 652 [424] pg/mL; $t_{120}=2.43$ [unequal variance]; $P=.02$) but not in the controls ($t_{70}=0.21$, $P=.84$). Because of these exploratory findings, we performed a more definitive 3-way factorial analysis of variance (ANOVA) (diagnosis × sex × age) with age stratified into 3 levels (40-60 years, 60-70 years, and older than 70 years). As expected, the results of the ANOVA revealed a significant difference by diagnosis of AD ($F_{1,191}=40.9$, $P<.001$) but no main level or interaction effects for the sex or age group variables (3-way ANOVA, $F_{2,191}=0.30$, $P=.74$). A similar 3-way ANOVA for CSF β-amyloid$_{1-42}$ also revealed a strong overall effect of AD diagnosis ($F_{1,191}=106.36$, $P<.001$) but no main

Table 1. Demographic Characteristics and Baseline Measures for Controls and Patients With Alzheimer Disease (AD)

	Controls (n = 72)	AD Participants (n = 131)	t (df)
Men/women	27/45	59/72	
Age, mean (SD), y	59.4 (8.5)	68.1 (9.1)	6.6 (201)
Education, mean (SD), y	16.7 (2.3)	14.7 (3.3)	−5.0 (189)*
MMSE score (0-30), mean (SD)	29.2 (1.1)	19.7 (6.7)	−15.2 (130)*
CDR score (0-3), mean (SD)	0	1.4 (0.7)	25.0 (130)*
GDS score (1-7), mean (SD)	1.0	4.3 (1.0)	35.3 (136)*
Duration of illness, mean (SD), y	NA	3.6 (2.4)	

Abbreviations: CDR, Clinical Dementia Rating; GDS, Global Deterioration Scale; MMSE, Mini-Mental State Examination; NA, not applicable.
*Satterthwaite adjusted t test scores of unequal variance. $P<.001$ for all t scores.

Figure 1. Scattergraphs of β-Amyloid$_{1-42}$ and Tau Levels in Cerebrospinal Fluid (CSF) for Controls and Patients With Alzheimer Disease



Boxes represent 25th, 50th, and 75th percentiles of the data. The length of the box is the interquartile range. The lower and upper whiskers represent the 25th and 75th percentile plus or minus 1.5 times the interquartile range, respectively.

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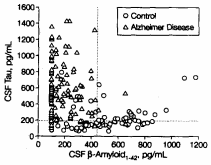
Figure 2. Specificity and Sensitivity Cutpoints for Measures of β-Amyloid$_{1-42}$ and Tau Levels in Cerebrospinal Fluid (CSF) Classifying Controls (n=72) and Patients With Alzheimer Disease (AD) (n=131)



Cutpoints are chosen for maximum separation of participant groups: upper left quadrant includes 120 participants with AD and 8 controls; upper right quadrant includes 3 participants with AD and 20 controls; lower left quadrant includes 7 participants with AD and 24 controls; and lower right quadrant includes 1 participant with AD and 20 controls. The cutpoints of 444 pg/mL for CSF β-amyloid$_{1-42}$ and 195 pg/mL for CSF tau generate a sensitivity of 92% and a specificity of 89%.

level or interaction effects for the sex or age group variables (3-way ANOVA, $F_{2,191}=0.57$, $P=.57$).

Neither CSF biomarker differed significantly by whether AD was confirmed by autopsy or clinically diagnosed (for mean [SD] CSF β-amyloid$_{1-42}$, 170 [115] pg/mL vs 187 [123] pg/mL, $t_{129}=0.68$, $P=.50$, respectively, and for mean [SD] CSF tau, 677 [250] pg/mL vs 559 [391] pg/mL, $t_{79}=-1.99$, $P=.06$, respectively). Therefore, the results of the 2 groups were combined.

Across all AD patients and controls, the CSF β-amyloid$_{1-42}$ and tau levels were significantly negatively correlated ($r=-0.30$, $P<.001$), perhaps a function of the number of AD patients with high CSF tau and low CSF β-amyloid$_{1-42}$ levels combined with the number of controls showing the opposite pattern. However, for the controls alone, the correlation between these 2 measures was positively correlated ($r=0.29$, $P=.02$), while for AD cases, the 2 measures were not correlated ($r=-0.08$, $P=.35$).

To determine whether changes in CSF β-amyloid$_{1-42}$ and CSF tau levels occur early in the onset of the disease, we tested for correlation between CSF β-amyloid$_{1-42}$ and tau measures and severity and duration of illness. Measures of CSF tau were significantly correlated with the CDR rating ($r=0.19$, $P=.03$) and MMSE score ($r=-0.20$, $P=.03$) and revealed a trend with the GDS score ($r=0.17$, $P=.053$), while CSF β-amyloid$_{1-42}$ levels showed a trend relationship with MMSE only ($r=0.16$, $P=.09$). Interestingly, years of education were associated with lower CSF tau levels in the overall AD group ($r=-0.19$, $P=.03$). Within the AD group, CSF β-amyloid$_{1-42}$ levels were not associated with age, age of onset, or duration of illness ($r=-0.14$, $P=.11$; $r=0.12$, $P=.18$; and $r=0.08$, $P=.35$, respectively). Similarly, CSF tau levels were not associated with age, age of onset, or duration of illness in the AD group ($r=-0.01$, $P=.90$; $r=0.01$, $P=.87$; and $r=-0.01$, $P=.90$, respectively). When patients with moderate and severe AD (CDR score of 2 or 3; n=56) were compared with controls, for both mean (SD) CSF β-amyloid$_{1-42}$ (175 [99] pg/mL vs 491 [245] pg/mL, $t_{99}=9.94$ [unequal variance], $P<.001$) and tau levels (660 [396] pg/mL vs 224 [156] pg/mL; $t_{68}=7.79$ [unequal variance], $P<.001$) were significantly different. When only patients with mild AD (CDR score of 0.5 or 1; n=75) were included, both mean (SD) CSF β-amyloid$_{1-42}$ (189 [135] pg/mL vs 491 [245] pg/mL; $t_{100}=9.21$ [unequal variance], $P<.001$) and tau levels (532 [333] pg/mL vs 224 [156] pg/mL; $t_{106}=7.22$ [unequal variance], $P<.001$) remained significantly different. While this analysis was exploratory, it suggests that changes in CSF β-amyloid$_{1-42}$ tau levels may be present early in the disease process.

CART Analysis

A CART analysis was performed to evaluate the combined contributions of CSF β-amyloid$_{1-42}$ and CSF tau to differentiate AD patients from controls. Cutpoints of 444 pg/mL for CSF β-amyloid$_{1-42}$ and 195 pg/mL for CSF tau maximized sensitivity to 92% and specificity to 82% in this analysis (FIGURE 2). These CART-defined cutpoints maximize the specificity and sensitivity for this particular group of participants, and would be lower in a new population.

Meta-Analysis

The meta-analysis of the literature on CSF β-amyloid$_{1-42}$ involved 17 studies that met criteria for inclusion (TABLE 2).[4-7,13,14,16,33-42] Other studies were reviewed[17,43-48] but they did not meet our criteria for the meta-analysis. Fourteen[4-7,13,14,16,33-39] of the 17 studies in the meta-analysis showed clear reductions in CSF β-amyloid$_{1-42}$ levels in AD vs control participants while 2 studies were equivocal and another reported changes in the opposite direction (Table 2 and FIGURE 3). The overall effect size (CSF β-amyloid$_{1-42}$ level difference between AD and control participants) of the meta-analysis with the previously published studies was 1.53 (95% confidence interval [CI], 1.39-1.69) (Figure 3). In the current study, the effect size was 1.76 (95% CI, 1.42-2.10). When the data from the current study are added to the meta-analysis (for a total of 18 studies), the effect size is 1.56 (95% CI, 1.43-1.69).

A similar meta-analysis was performed for 34 studies on CSF tau in the literature search (TABLE 3 and FIGURE 4).[4,5,7,10,11,14,36,40,4149-72] All the studies report a significant difference in CSF tau levels between AD participants and controls. For the combined series of previously published studies, the overall effect size was 1.31 (95% CI, 1.23-1.39). The overall effect size of the current study was 1.18 (95% CI, 0.87-1.49). When all 35 studies are included in the meta-analysis (ie, 34 studies and the current study), the effect size remains 1.31 (95% CI, 1.23-1.39).

COMMENT

The idea that CSF β-amyloid$_{1-42}$ and tau levels could be useful in diagnosing AD is not new. Numerous authors have documented the changes of these biomarkers in AD patients vs controls,[4-6,13,33] but not without controversy, especially with respect to CSF β-amyloid$_{1-42}$ levels. While most studies show a decrease of CSF

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Table 2. Meta-analysis of 17 Studies With Participants With Alzheimer Disease (AD) and Controls Compared With the Current Study for Cerebrospinal Fluid (CSF) Measures of β-Amyloid$_{1-42}$ Levels

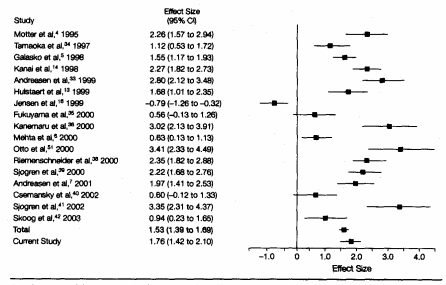
	AD Group		Control Group			
Study	No. of Study Participants	CSF β-Amyloid, Mean (SD), pg/mL	No. of Study Controls	CSF β-Amyloid, Mean (SD), pg/mL	*t* (*df*)*	*P* Value
Motter et al,[4] 1995	37	383 (76)	20	632 (156)	6.72 (24)	<.001
Tamaoka et al,[34] 1997	20	738 (374)	34	1450 (743)	4.67 (51)	<.001
Galasko et al,[5] 1998	82	833 (379)	60	1485 (473)	8.81 (110)	<.001
Kanai et al,[14] 1998	93	495 (164)	41	1090 (405)	9.08 (46)	<.001
Andreasen et al,[35] 1999	53	709 (304)	21	1678 (436)	9.33 (28)	<.001
Hulstaert et al,[13] 1999	84	522 (197)	11	874 (293)	3.87 (11)	.003
Jensen et al,[15] 1999	80	536 (284)	24	333 (135)	−4.83 (82)	<.001
Fukuyama et al,[36] 2000	23	331 (188)	13	626 (909)	1.16 (13)	.27
Kanemaru et al,[38] 2000	24	284 (92)	19	714 (188)	9.14 (25)	<.001
Mehta et al,[6] 2000	36	60 (78)	29	147 (188)	2.34 (36)	.02
Otto et al,[37] 2000	14	361 (153)	20	903 (163)	9.89 (29)	<.001
Riemenschneider et al,[39] 2000	75	455 (210)	30	916 (160)	12.14 (70)	<.001
Sjogren et al,[39] 2000	60	381 (127)	32	772 (244)	8.47 (40)	<.001
Andreasen et al,[7] 2001	105	523 (180)	18	897 (242)	6.27 (20)	<.001
Csernansky et al,[40] 2002	32	1777 (1055)	10	2400 (1030)	1.68 (15)	.11
Sjogren et al,[41] 2002	19	411 (99)	17	853 (161)	9.78 (26)	<.001
Skoog et al,[42] 2003	12	389 (161)	28	657 (320)	3.44 (36)	.002
Total No.	**849**	**554 (300)†**	**427**	**979 (419)†**		
Current study	131	183 (121)	72	491 (245)	10.02 (90)	<.001

*Weighted average and variance across all studies.
†Satterthwaite adjusted *t* test scores of unequal variance.

β-amyloid$_{1-42}$ levels in AD patients vs controls, a small number of studies have shown no changes or even elevations of the protein levels.[16,17,43,73] Given the range of methods used and the variable sample sizes of the studies, this result is perhaps not surprising, but it has left open the question of whether and when changes in CSF β-amyloid$_{1-42}$ levels are manifest in AD. To our knowledge, our study is the largest to confirm the decrease of CSF β-amyloid$_{1-42}$ and an increase in tau levels in AD participants. In addition, these differences appear to be found in patients with mild AD as well in patients with moderate to severe AD.

Two possible confounding factors within the current study deserve further explanation. First, the age of the controls is significantly lower than that of the AD patients. While this factor was not significantly associated with CSF β-amyloid$_{1-42}$ levels for either AD patients or controls, an age effect was found within the controls for CSF tau. However, after controlling for age, CSF tau levels remained significantly higher in the AD group vs controls. Second, freezer shelf life might be a factor in the assay values, as the CSF samples from AD patients had been frozen longer than the samples from controls. However, no relationship was found between CSF β-amyloid$_{1-42}$ or tau

Figure 3. Effect Sizes of Results from 17 Studies of Meta-analysis of Measures of β-Amyloid$_{1-42}$ in Cerebrospinal Fluid (CSF) for Controls and Participants With Alzheimer Disease (AD)



CI indicates confidence interval. Effect size is the difference in means between AD patients and controls divided by the pooled SD.

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levels and shelf life for either the AD patients or controls.

CSF Tau and β-Amyloid$_{1-42}$ in AD

Some authors have found a modest correlation between CSF tau and baseline clinical measures,[55,74,75] while others, including our own group, have reported no significant relationship.[4,12,57] The lack of correlation may have been due in part to the relatively restricted range of dementia severity in some of these studies. In our current study, with a much larger sample population of AD patients, we found a small but statistically significant correlation between CSF tau levels and several of the global severity measures, including the CDR, GDS, and MMSE ratings. Also of interest, CSF tau levels were inversely correlated with education level, suggesting a possible protective factor. Conversely, analysis of CSF β-amyloid$_{1-42}$ levels revealed only a modest trend for a correlation with MMSE score in the AD patients, and no significant relationship was found with age, other severity measures of dementia, or CSF tau levels. While a significant correlation exists between CSF β-amyloid$_{1-42}$ and tau levels across all participants tested, this correlation did not persist within the AD population alone, perhaps reflecting the

Table 3. Meta-analysis of 34 Studies With Participants With Alzheimer Disease (AD) and Controls Compared With the Current Study for Cerebrospinal Fluid (CSF) Measures of Tau Protein Levels

	AD Group		Control Group			
Study	No. of Study Participants	CSF Tau, Mean (SD), pg/mL	No. of Study Controls	CSF Tau, Mean (SD), pg/mL	t (df)*	P Value
Vandermeeren et al,[49] 1993	27	10.9 (4.9)	51	0.1 (0.5)	11.42 (26)	<.001
Arai et al,[50] 1995	70	77 (46)	19	9 (5)	12.11 (75)	<.001
Blennow et al,[51] 1995	44	524 (280)	31	185 (50)	7.86 (47)	<.001
Mori et al,[52] 1995	14	820 (90)	36	380 (120)	14.07 (32)	<.001
Munroe et al,[53] 1995	24	1430 (739)	14	816 (355)	3.45 (35)	.002
Motter et al,[4] 1995	37	407 (241)	20	212 (102)	4.27 (53)	<.001
Skoog et al,[54] 1995	11	254 (113)	36	171 (78)	2.28 (13)	.04
Tato et al,[55] 1995	23	279 (100)	23	26 (11)	12.06 (23)	<.001
Vigo-Pelfrey et al,[56] 1995	71	361 (166)	26	190 (80)	6.79 (88)	<.001
Arai et al,[57] 1997	17	95 (44)	15	19 (15)	6.69 (20)	<.001
Golombowski et al,[58] 1997	19	53 (39)	12	31 (17)	2.16 (27)	.04
Andreasen et al,[59] 1998	43	796 (382)	18	190 (57)	10.14 (46)	<.001
Arai et al,[60] 1998	69	90 (45)	17	20 (13)	11.17 (82)	<.001
Galasko et al,[3] 1998	82	663 (481)	60	387 (167)	4.81 (106)	<.001
Kanai et al,[14] 1998	93	489 (298)	41	217 (128)	7.4 (132)	<.001
Kurz et al,[61] 1998	40	697 (447)	36	169 (64)	7.39 (41)	<.001
Mecocci et al,[62] 1998	29	436 (360)	23	212 (200)	2.84 (45)	.007
Nishimura et al,[63] 1998	163	426 (234)	65	188 (103)	10.65 (224)	<.001
Shoji et al,[64] 1998	55	467 (285)	34	218 (139)	5.51 (83)	<.001
Andreasen et al,[65] 1999	274	690 (341)	65	227 (101)	19.2 (324)	<.001
Burger et al,[66] 1999	38	580 (370)	28	273 (203)	4.31 (60)	<.001
Green et al,[67] 1999	17	802 (381)	9	198 (49)	6.44 (17)	<.001
Hampel et al,[68] 1999	25	566 (329)	19	245 (154)	4.3 (36)	<.001
Molina et al,[69] 1999	83	522 (290)	8	216 (150)	4.95 (13)	<.001
Kahle et al,[70] 2000	30	840 (560)	16	340 (230)	4.26 (42)	<.001
Kanemaru et al,[36] 2000	24	460 (301)	19	115 (76)	5.4 (27)	<.001
Sjoegren et al,[26] 2000	60	743 (503)	32	307 (168)	6.11 (80)	<.001
Andreasen et al,[7] 2001	105	759 (417)	18	264 (102)	10.47 (108)	<.001
Hampel et al,[71] 2001	17	496 (205)	12	312 (98)	3.22 (24)	.004
Itoh et al,[10] 2001	236	450 (252)	95	149 (107)	15.25 (328)	<.001
Roesler et al,[72] 2001	27	761 (407)	17	224 (81)	6.65 (29)	<.001
Shoji et al,[11] 2002	366	482 (271)	113	186 (107)	17.03 (452)	<.001
Sjogren et al,[4] 2002	19	919 (349)	17	342 (116)	6.80 (22)	<.001
Csernansky et al,[40] 2002	32	1260 (460)	10	800 (280)	3.98 (28)	<.001
Total No.	**2284**	**534 (317)†**	**1054**	**212 (122)†**		
Current study	131	587 (365)	72	224 (156)	9.8 (192)	<.001

*Weighted average and variance across all studies.
†Satterthwaite adjusted t test scores of unequal variance.

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restricted range of the CSF values in the AD patients in this study.

Meta-analysis

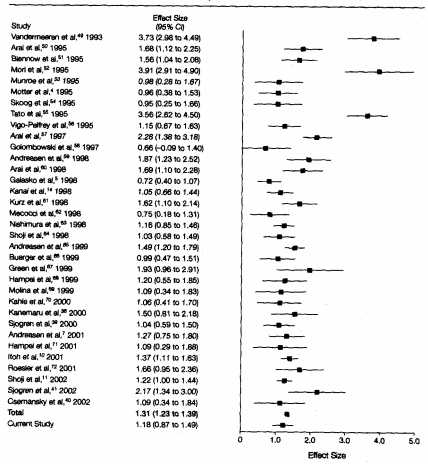
A meta-analysis was performed with published studies of CSF β-amyloid$_{1-42}$ in AD to elucidate the overall trends in the data and to determine the effect size of group differences. Not all the available studies were amenable to the meta-analysis method, but we did find 17 studies that met the criteria (Table 2 and Figure 3). The considerable variability in mean values among the studies highlights the lack of standardization of assay methods among centers and is of some concern. However, with 14 of the 17 studies showing significant reductions in CSF β-amyloid$_{1-42}$ levels in the AD vs control participants, the result of the meta-analysis was unequivocal and the effect size quite large, with AD participants showing a lower CSF β-amyloid$_{1-42}$ level. The direction and effect size of our current study was consistent with the meta-analysis, indicating a similar trend. For the meta-analysis of studies on CSF tau, the data are even more unequivocal (Table 3 and Figure 4). Despite differences in baseline levels across studies, the pattern of change is uniform; all previous studies report AD patients having higher CSF tau levels than that found with controls.

With the general consistency in the literature for CSF β-amyloid$_{1-42}$ and tau, it is not surprising that several companies have initiated commercial tests of these measures for clinical use with individual patients (Athena Diagnostics, Worcester, Mass; Innogenetics, Ghent, Belgium; and ABETA GmbH, Heidelberg, Germany). However, the claims regarding sensitivity and specificity from the commercial concerns and our own CART analysis are derived from clinically diagnosed AD cases in which the diagnostic accuracy already approximates 85% when validated by the standard pathologic diagnosis at autopsy.[25,76,77] Furthermore, the cutpoints for most sensitivity and specificity assessments are chosen to maximize the specificity and sensitivity results with those measures. Our data are fairly representative of the literature and clearly show considerable variance in the data that provides room for misclassification by an individual biomarker, whether the marker is CSF β-amyloid$_{1-42}$ or CSF tau (Figure 1).

Approach to Clinical Application

Given the overlap between AD and control groups, it is evident that the diagnostic sensitivity and specificity of these individual CSF β-amyloid$_{1-42}$ and tau assays is simply not sufficient to warrant general clinical use of these biomarkers for individual use. Nonetheless, when the CSF β-amyloid$_{1-42}$ and tau data are combined into 1 statistical analysis, the overlap with clinical diagnoses generally improves.[4,5,7] While the differences in CSF levels between AD populations and controls are indeed impressive, the interpretations of this data are limited because they result from contrasts of starkly different populations (ie, AD vs healthy, self-selected controls). This type of artificial contrast is not representative of realistic clinical comparisons and is considered phase 1 diagnostic testing.[78] A truer test of any suggested diagnostic marker would include comparisons among populations with different types of dementia, including vascular, Lewy body dementia, and other neurological disorders, or cases with very early cognitive impairment. It is likely

Figure 4. Effect Sizes of Results from 34 Studies of Meta-analysis of Measures of Tau Protein in Cerebrospinal Fluid for Controls and Participants With Alzheimer Disease (AD)



CI indicates confidence interval. Effect size is the difference in means between AD patients and controls divided by the pooled SD.

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that this phase 2 testing with populations with mixed diagnoses will show poorer sensitivity and specificity results, and this approach has previously been attempted with only modest success.[7] Thus, while it can be said that these research diagnostic techniques are indeed improving, a great deal of developmental testing is still in order at the interface of clinical medicine and research methodology.[7,8]

Perhaps the biggest future challenge to the research in AD will be to standardize these CSF measures across numerous centers and then apply them as part of a prospective clinical evaluation of participants who are at risk for developing AD. Currently, a clinical criterion standard is not available to help with the early diagnosis of AD. As a result, analysis of CSF β-amyloid$_{1-42}$ and tau levels are likely to be most useful diagnostically when they are used in conjunction with other biomarkers, including structural magnetic resonance imaging, genetic markers, and positron-emission tomography scans when a tracer for β-amyloid burden is more readily available. This approach is the focus of an ongoing longitudinal, prospective study at the National Institute of Mental Health with a cohort of older controls (protocol 95-M-96).

Conclusion

The study of CSF biomarkers, such as β-amyloid$_{1-42}$ and tau, in AD participants is emerging as an important but still nascent field.[9] The cross-sectional data clearly show group differences between AD participants and controls, both in this large study and in a meta-analysis of the literature. However, these studies represent the early development of diagnostic measures. Additional studies are required to establish methodologic standardization in the CSF assays across centers and to see if a specificity for AD exists over other forms of dementia, which have substantial overlap with AD at postmortem (ie, Lewy body dementia or cerebrovascular dementia). Furthermore, the mixed findings in the literature relating these CSF biomarkers to clinical severity measures of dementia suggest the need for larger sample sizes to establish statistical significance. The reason for the varying data may be because single biomarkers may not be able to provide an accurate reflection of the pathologic process across the entire span of the illness. Rather, individual biomarkers may be correlated to the prominent pathophysiology of a particular stage of the illness but not to the pathophysiology of earlier or later stages.

Perhaps the most important future use for such biomarkers is in the prospective study of participants at risk for developing AD. However, much work is needed with the standardization of assay methods before prognostic significance can be attributed to these biomarkers. Once an individual's normal levels of the biomarkers are well established, it is possible that gradual changes in these levels (eg, CSF levels of β-amyloid$_{1-42}$ or tau) could eventually be interpreted as suggestive evidence of incipient AD. To test this hypothesis, longitudinal prospective studies of controls and early AD participants are necessary and are currently ongoing.

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Author Contributions: *Study concept and design:* Sunderland, Mirza, Putnam, Bergeson, Cohen.
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Drafting of the manuscript: Sunderland, Putnam, Manetti, Cohen.
Critical revision of the manuscript for important intellectual content: Sunderland, Linker, Mirza, Friedman, Bergeson, Zimmermann, Tang, Bartko.
Statistical expertise: Putnam, Zimmermann, Bartko, Cohen.
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Study supervision: Sunderland, Mirza, Bergeson.
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Tab 19

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BUD ALBRIGHT, STAFF DIRECTOR

ONE HUNDRED NINTH CONGRESS

U.S. House of Representatives
Committee on Energy and Commerce
Washington, DC 20515–6115

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January 24, 2006

The Honorable Elias Zerhouni, M.D.
Director
National Institutes of Health
9000 Rockville Pike
Bethesda, MD 20892

Dear Dr. Zerhouni:

The Committee on Energy and Commerce is continuing its investigation of the adequacy of the National Institutes of Health (NIH) policies for maintaining research samples of human tissue. In response to the Committee's June 20, 2005 letter and subsequent communications with Committee staff, the NIH initially provided records on August 15, 2005.

One subject area of the Committee's June 20th request concerned the disposition of spinal fluid samples from patients with Alzheimer's disease and control subjects collected by scientists at the National Institute of Mental Health (NIMH) to be used in studies involving lithium. After the August 15, 2005 production, the Committee staff alerted the NIH that it appeared that not all responsive documents concerning these samples and the lithium study had been provided to the Committee. After the Committee staff raised these concerns with the NIH about the production, the Committee did receive additional responsive records: three sets of records over the last few months from the NIH related to the spinal fluid samples and the lithium study, with the last set received on January 4, 2006. We are troubled that the NIH did not produce all the responsive records in the first production, and produced these records only after Committee staff pressed several times for these additional responsive records.

Furthermore, these additional records raise questions about the disposition of the spinal fluid samples, the nature of NIMH oversight over human samples, and the way NIH/NIMH handled the Committee's request for records relating to the lithium study.

Pursuant to Rules X and XI of the U.S. House of Representatives, please provide the following by February 6, 2006:

1. All records relating to responses by NIH, and/or any component of NIH including NIMH, to the Committee's June 20, 2005 request letter and/or subsequent communications with the Committee staff relating to the June 20, 2005 letter, including memoranda to file.

2. All records relating to the April 1998 PHS Material Transfer Agreement (MTA) between a scientist at NIMH and a drug company collaborator, including but not limited to communications between any individual at NIMH and any individual employee of the drug company collaborator relating to Alzheimer's Disease research since January 1, 1997. This request includes all records relating to the approval of the April 1998 MTA.

3. According to a record provided by the NIH, the following protocol numbers of studies were listed in association with spinal fluid samples provided through the NIH-approved MTA: 95-M-0096, 82-M-0123, 78-M-0148, 95-M-0025, 85-M-0207, 88-M-0009, 88-M-0076, 88-M-0126, 91-M-0194, 97-M-0157, 01-M-0128, and 02-M-0305. Please confirm that the NIH-approved MTA in connection with these spinal fluid samples is the April 1998 Material Transfer Agreement. For each of studies represented by the afore-mentioned protocol numbers, please provide: (a) the name(s) of the Principal Investigator(s) for each study, and the name(s) of the tissue collector, if different; (b) the nature and purpose(s) for collecting the spinal fluid samples; (c) the name of the NIH office serving as the repository storage site, and the data management center, if different; (d) the name, title, office, and address of each recipient investigator; and (e) all records relating to the samples collected, including but not limited to copies of the protocols and copies of the informed consent forms.

4. Excluding records responsive to Item 2, all records relating to communications regarding the transfer of the spinal fluid samples (identified by the protocol numbers of the studies listed in Item 3) for new research uses.

5. What authority is required at NIH for a new research use of human samples previously collected for a prior intramural research study at NIH? Does the answer to this question vary by Institute/Center? If so, please explain. Please provide all records relating to authorization, if any, by the NIH's Office of Human Subjects Research (OSHR) or an NIH Institutional Review Board, for the use of human samples in the April 1998 MTA. Please provide all records relating to authorization for the new research use of human samples in the April 1998 MTA.

Please note that, for the purpose of responding to these requests, the terms "records" and "relating" should be interpreted in accordance with the attachment to this letter. In addition, we are requesting that following production of the records to the Committee, you make available NIH employees for Committee staff interviews as requested by Committee staff.

If you have any questions, please contact Alan Slobodin of the Majority Committee staff at (202) 225-2927 and David Nelson of the Minority Committee staff at (202) 226-3400.

Sincerely,

Joe Barton
Chairman

John D. Dingell
Ranking Member

Ed Whitfield
Chairman
Subcommittee on Oversight
and Investigations

Bart Stupak
Ranking Member
Subcommittee on Oversight
and Investigations

Attachment

ATTACHMENT

1. The term "records" is to be construed in the broadest sense and shall mean any written or graphic material, however produced or reproduced, of any kind or description, consisting of the original and any non-identical copy (whether different from the original because of notes made on or attached to such copy or otherwise) and drafts and both sides thereof, whether printed or recorded electronically or magnetically or stored in any type of data bank, including, but not limited to, the following: correspondence, memoranda, records, summaries of personal conversations or interviews, minutes or records of meetings or conferences, opinions or reports of consultants, projections, statistical statements, drafts, contracts, agreements, purchase orders, invoices, confirmations, telegraphs, telexes, agendas, books, notes, pamphlets, periodicals, reports, studies, evaluations, opinions, logs, diaries, desk calendars, appointment books, tape recordings, video recordings, e-mails, voice mails, computer tapes, or other computer stored matter, magnetic tapes, microfilm, microfiche, punch cards, all other records kept by electronic, photographic, or mechanical means, charts, photographs, notebooks, drawings, plans, inter-office communications, intra-office and intra-departmental communications, transcripts, checks and canceled checks, bank statements, ledgers, books, records or statements of accounts, and papers and things similar to any of the foregoing, however denominated.

2. The terms "relating," "relate," or "regarding" as to any given subject means anything that constitutes, contains, embodies, identifies, deals with, or is in any manner whatsoever pertinent to that subject, including but not limited to records concerning the preparation of other records.

Tab 20

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U.S. House of Representatives
Committee on Energy and Commerce
Washington, DC 20515–6115

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June 20, 2005

The Honorable Elias Zerhouni, M.D.
Director
National Institutes of Health
9000 Rockville Pike
Bethesda, MD 20892

Dear Dr. Zerhouni:

The Committee on Energy and Commerce is investigating the adequacy of the National Institutes of Health (NIH) policies for maintaining research samples of human tissue.

Our interest in the NIH's maintaining of human tissue samples arises from concerns raised by a scientist at NIH ("NIH scientist"). She contacted the Committee staff about the problems she encountered in locating spinal fluid samples she and her colleagues had collected from over 30 patients with Alzheimer's disease.

The NIH scientist had previously worked at the National Institute of Mental Health (NIMH) with the Geriatric Psychiatry Group. She left the NIMH in 1997, and returned to NIH at another institute/center in August 2001. Prior to leaving the NIMH in 1997, she was the principal investigator on drug studies in which she and other colleagues collected spinal fluid from over 30 Alzheimer's patients. Approximately 20 ccs of spinal fluid were collected with each spinal tap. The NIH scientist left the NIMH before conducting these studies and did not use the spinal fluid samples. According to the NIH scientist, these spinal fluid samples were stored in appropriately backed-up freezers when she left NIMH in 1997.

Sometime in mid-2004, the NIH scientist, now at another NIH institute/center, asked her former supervisor at NIMH for these patient samples for a study she wanted to conduct. After several months, the former supervisor in January 2005 reported to the NIH scientist that his group would be able to produce 10 subjects total (before and after taps) with only 0.5 cc

available for most of the subjects. The former supervisor and the NIMH have been unable to account for what happened to the rest of the spinal fluid samples.

The Committee staff has learned from NIH officials that the NIH has no uniform, centralized, and mandatory authority regulating the handling of human tissue samples. Some NIH laboratories keep a written record on the maintenance of these samples, but other NIH laboratories do not. Although there are explicit regulations defined in 42 C.F.R. 72.6 detailing the handling for hazardous biological materials and select agents, there is no explicit policy for the handling and accounting of human tissue samples. In addition, there is no formal inventory control or tracking system at NIH. If a freezer or other storage facility malfunctions and the human tissue samples become unusable, NIH laboratories are not required to account for the disposition of these samples. There is reason to believe that there are cases where NIH loses human tissue samples but has no record of what has been lost. Moreover, the lack of accountability leaves NIH wholly vulnerable to theft and diversion of valuable human tissue samples.

We are extremely concerned over what was described to Committee staff by NIH officials of a fairly loose, ad-hoc approach to controlling human tissue samples. These samples were collected under informed consent from human subjects who agreed to provide their tissue because they were told that the sample would be used for a particular purpose in the study, perhaps even used to look at the effects from a particular drug. Some of these samples are extraordinarily precious from a research standpoint because some patients who donated samples had a rare disease. For example, we note that the National Institute of Allergy and Infectious Diseases obtained blood samples from SARS patients as part of its immunological research of SARS and coronaviruses. In addition, NIH intramural researchers sometimes rely on obtaining human tissue samples from sources outside NIH for their laboratory work, or even in their work for Cooperative Research and Development Agreements with third parties.

NIH has an obligation to the human subjects and the outside scientific community to require an appropriate tracking system or protocol for all laboratories involved with collection and maintenance of human tissue samples. NIH officials acknowledged to Committee staff the importance of maintaining human research samples because for all published work, scientists are expected to provide access to other researchers to the human tissue samples for the purpose of reproducing the results reached in the scientist's reported study.

In light of the concerns about the current handling by NIH of human tissue samples, pursuant to Rules X and XI of the U.S. House of Representatives, please provide the following by no later than Tuesday, July 5, 2005:

1. The current total number of human tissue samples maintained at NIH, with a breakdown for each Institute or Center. The current total number of laboratories at NIH that maintain human tissue samples and the current total number of laboratories that have a tracking system accounting in place for the human tissue samples.

2. All records dated on or since January 1, 2002, in possession of NIH, including communications within each Institute/Center and each laboratory, relating to any distinct direction, instruction, or policy relating to the handling of human tissue samples.

3. All records dated on or since January 1, 2002, in possession of the NIH Office of Intramural Research or the NIH Office of Management Assessment relating to any closed investigation of an allegation relating to the handling or accounting of human tissue samples. Please also state whether there are any open investigations and, if so, which institutes or centers are under investigation.

4. The current total amount of expenditures for FY2005 by NIH for maintaining and repairing freezers or other storage facilities containing human tissue samples.

5. An estimate of the total number of human tissue samples lost each year at NIH laboratories, and an estimate of the number of human tissue samples lost each year at NIH laboratories because of freezer or storage facility malfunctions.

6. A description of any measures NIH is taking to reduce the number of research freezer or other storage facility malfunctions or breakdowns.

7. List the names of the ten rarest diseases for which NIH has human tissue samples, the name of the Institute and laboratory that has possession of these samples, and the specific measures currently being taken to track these samples.

8. All records relating to the CSF samples collected by the NIH scientist and others in a NIMH study on lithium in early Alzheimer's disease patients. Patient identifiers may be redacted.

Additionally, please provide the following:

9. Since January 1, 1995, has any official at NIH authorized the use of human tissue samples in possession of NIH to be used by any NIH employee in support of an outside activity?

10. Since January 1, 1995, has any official at NIH ever used human tissue samples that were in possession of NIH in connection with any of his or her outside activities?

Please note that, for the purpose of responding to these requests, the terms "records" and "relating" should be interpreted in accordance with the attachment to this letter. In addition, we are requesting that following production of the records to the Committee, you make available NIH employees for Committee staff interviews as requested by Committee staff.

If you have any questions, please contact Alan Slobodin of the Majority Committee staff at (202) 225-2927 and David Nelson of the Minority Committee staff at (202) 226-3400.

Sincerely,

Joe Barton
Chairman

John D. Dingell
Ranking Member

Ed Whitfield
Chairman
Subcommittee on Oversight
and Investigations

Bart Stupak
Ranking Member
Subcommittee on Oversight
and Investigations

Attachment

ATTACHMENT

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2. The terms "relating," "relate," or "regarding" as to any given subject means anything that constitutes, contains, embodies, identifies, deals with, or is in any manner whatsoever pertinent to that subject, including but not limited to records concerning the preparation of other records.

Tab 21

Donnelly, Jon (NIH/OD)

From: Putnam, Karen T. (NIH/NIMH)
Sent: Tuesday, December 07, 2004 5:13 PM
To: Donnelly, Jon (NIH/OD)
Subject: Requested Summary

Dear Mr. Donnelly,

Please receive the attached document to the information requested by email on November 23, 2004 from the NIH Ethics Office.

Thank you
Karen Putnam

From: Donnelly, Jon (NIH/OD)
Sent: Tuesday, November 23, 2004 5:27 PM
To: Putnam, Karen T. (NIH/NIMH)
Subject: Your Activities with Pfizer

Dear Dr. Putnam:

As you are aware, the NIH Office of Management Assessment (OMA) is conducting a review of your outside activities with Pfizer, where you served as a consultant from 1/1/2001 to 8/13/2002, from 1/1/2003 to 1/1/2004, and from 1/1/2004 to the present. (Please clarify the dates that we have for your service with the organization, if they are not correct.) The NIH Ethics Office is working with OMA to review whether, if at all, your engaging in these activities violated provisions of the ethics laws and regulations. To that end, it is necessary to determine whether these activities significantly overlapped with your official duties. To help us make that determination, please prepare a short (one page should be sufficient) summary of the nature of the activities and the nature of your official responsibilities at the time of the outside activities.

Please provide as much detail as possible on the scientific subject matter of the activities and the scientific subject matter of your official responsibilities during the timeframe in which you were participating in the activities at issue. If there is any overlap between the subject matter of your official duties and the outside activities, please address those similarities. If the activities are distinct in subject matter from your official duties, please explain how the matters are distinct. In addition, please clearly state the scope of your involvement with the organization. For example, if your service with Pfizer was limited to a specific project, you should explain your specific responsibilities. If your service with Pfizer was more general and broad, you should fully describe your areas of responsibility, whatever they were at the time.

The summary that you provide will be evaluated by a panel of IC Directors, who have been asked to reach a conclusion as to the amount of overlap between your consulting activities with Pfizer and your official duties at the time of the activities. The process for handling the results of all reviews in these matters is under development and will be communicated to all involved at the conclusion of NIH's reviews.

Please provide the requested summary by Wednesday, December 1, 2004. You may e-mail it to me directly if you wish.

If you have any questions about this request, please contact me immediately.

Sincerely,
Jon Donnelly, J.D.
NIH Ethics Office
301-402-6628

05/19/2008 15:08 FAX 005/008

Tab 22

REQUEST FOR SHIPMENT

Serial No. 366204

Instructions:
Requesting Office sends the first two copies (white and yellow) to the Shipping Officer. Keep the third (pink) copy for reference.
Shipping Officer - After carrier has picked up the shipment, file this form to back up authorization for shipment.

NOTE: All dutiable international shipments (other than printed documents) must be accompanied by three copies of a commercial invoice (NIH 1884-1) for customs clearance.

1. We are requesting shipment of: ☒ Government-owned property ☐ Other:
2. Date of request: 2-2-00
3. Requestor's Name (Consignor): Frey, Sunder [illegible] MD
4. ICD: MH-BP
5. Building and Room: 11A N22
6. Phone No.: 496-1948
7. Shipment to be paid by: ☒ NIH ☐ Consignee (If consignee, complete item 8.)
8. Carrier's Name; Account No. to Be Billed; Consignee's Phone No.

9. DESCRIPTION OF ARTICLES When items of varying descriptions are to be shipped, separate them and enter the quantity and value of each. If any item is hazardous or infectious to humans, note the amount (in milliliters or kilograms) and give a detailed description of the substance.	10. HAZARDOUS or INFECTIOUS?	11. QTY.	12. DOLLAR VALUE
Samples in dry ice.			
9.K2			
	TOTALS ▶		$

13. Packaging: ☐ Packed by requestor ☐ To be packed by Shipping (Nonperishable, nonhazardous items only)

14. If material was packed by the requestor, AND it is biological material, how was it packed? ☒ Dry ice ☐ Ice packs ☐ Other: ☐ Wet ice ☐ Room temperature

15. SHIP TO: (Consignee)
(Name, street address, city, state or country, zip code, telephone number)
(Do not use P.O. box addresses)
David Friedman MD
Pfizer Gen Research (860-441-[illegible] phone)
Eastern Point Rd, Bldg 118-C-2 06355

16. Additional information, instructions, or justification

17. Date shipment must arrive at destination: 2-3-00

18. Property clearance (Signature of Property Accountable Officer or other official)

19. Common Account Number (CAN): 83376.47

20. Administrative Officer's name (Typed): Pam Fitzgerald

21. AO's signature

SHIPPING OFFICER COMPLETES THIS SECTION

22. Carrier	23. Date shipped	24. GBL or ROC number	25. Airway bill or freight bill number
26. UPS Charge	**27. Packed by owner**	**28. Packed by shipping**	**29. ☐ Internat. ☐ Domestic** / **30. Mode**
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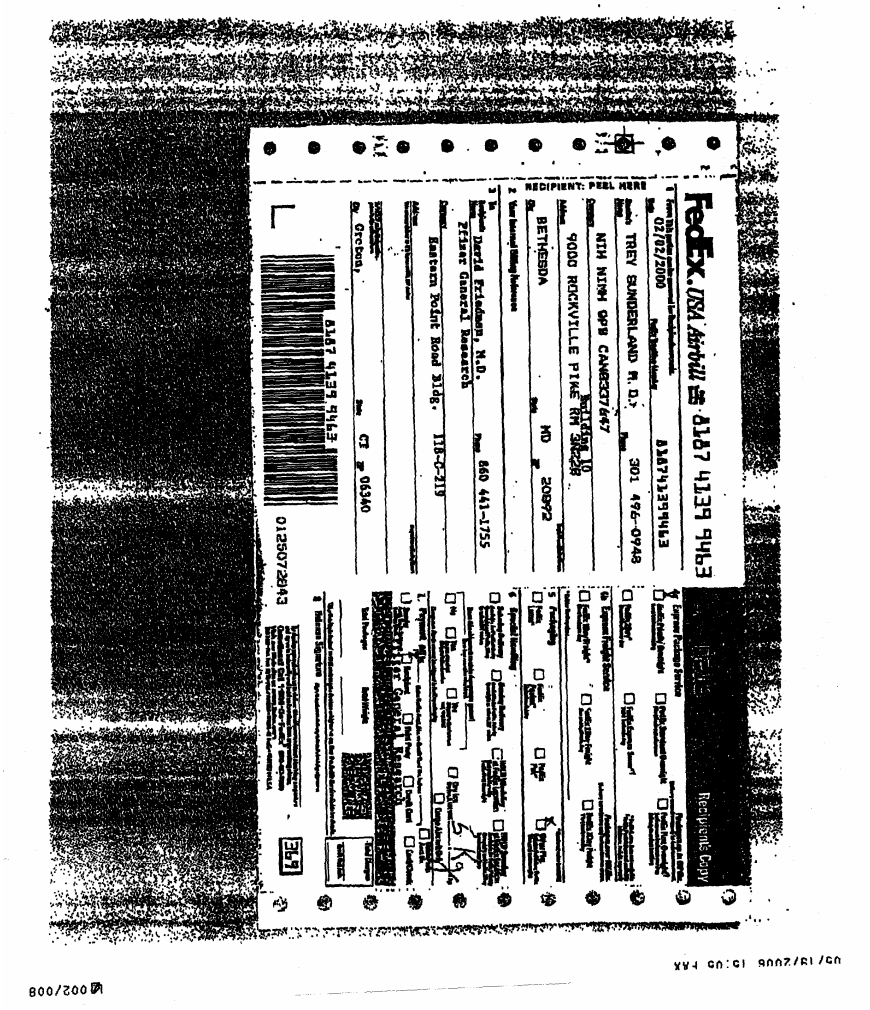
NIH 1664 (Rev. 10/90)

Shipping 65924 GY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Pfizer General Research
860 441-1755
Eastern Point Road Bldg. 118-C-219
Groton,
CT
06340
8187 4139 9463
0125072943

Tab 23

cc:Mail for: kathryn e smith

Subject: Sunderland and OGS
From: Kathryn E Smith 6/9/98 12:37 PM
To: Roy Mansfield at CR_SAND_08
To: Liam Ratcliffe at CR_SAND_03
To: B Michael Silber at CR_GROTON_NONCLIN25
To: Kathryn E Smith
To: W Frost White at CR_GROTON_NONCLIN15
To: Stephen A. Williams at CR_GROTON_CLIN01

ENTERED
NIMH

For your information, Dr Trey Sunderland at NIH (our source for the AD samples) has requested that we do not mention him in any publicity concerning his involvement in our OGS collaboration. Of course, the only publicity would occur with both Pfizer and OGS approval but I wanted to make sure that you all knew so that there be no confusion.

Thanks

Kathy

c/f OGS

CONFIDENTIAL
NOT FOR PUBLIC DISCLOSURE/FOIA EXEMPT

Tab 24 CR & AMENDMENT 5/20/04

CLINICAL RESEARCH PROTOCOL: **CONTINUING** REVIEW APPLICATION	PROTOCOL NO. 01-M-0128	PRINCIPAL INVESTIGATOR (Print or Type Name): Trey Sunderland, M.D.

PROTOCOL TITLE: Versus Anti-Inflammatory (N.A)
Pilot Study of Immunomodulatory Therapy in Alzheimer's Disease

ION REQUESTED:
- ☒ Renew -New subject accrual to continue
- ☐ Renew -Enrolled subject followup only
- ☐ Terminate-Protocol discontinued (describe briefly in the attached narrative.)

HAVE THERE BEEN ANY AMENDMENTS SINCE THE LAST REVIEW?
- ☐ No
- ☒ Yes (Describe briefly in the attached narrative)

SUMMARY OF PROTOCOL SUBJECTS:
- 60 Accrual ceiling set by IRB
- 6 New subjects accrued since last review
- 21 Total subjects accrued since protocol began (If accrual has been less than expected, discuss in the attached narrative)

ACCRUAL EXCLUSIONS:
- ☒ None ☐ Male
- ☐ Female ☐ Other: _____

IMPAIRED SUBJECTS:
- ☐ None ☐ Physically ☒ Cognitively

HAVE THERE BEEN ANY CHANGES IN THE SUBJECT POPULATION, RECRUITMENT OR SELECTION CRITERIA SINCE THE LAST REVIEW?
- ☒ No
- ☐ Yes (Explain changes in the attached narrative)

HAVE THERE BEEN ANY CHANGES IN THE INFORMED CONSENT PROCESS OR DOCUMENTATION SINCE THE LAST REVIEW?
- ☐ No
- ☒ Yes (Explain changes in the attached narrative)

"AS ANY INFORMATION APPEARED IN THE LITERATURE, OR EVOLVED M THIS OR SIMILAR RESEARCH, THAT MIGHT AFFECT THE IRB's UATION OF THE RISK/BENEFIT ANALYSIS OF HUMAN SUBJECTS OLVED IN THIS PROTOCOL?
- ☒ No
- ☐ Yes (Discuss in the attached narrative)

HAVE ANY UNEXPECTED COMPLICATIONS OR SIDE EFFECTS BEEN NOTED SINCE LAST REVIEW?
- ☐ No
- ☒ Yes (Identify and explain in attached narrative)

HAVE ANY SUBJECTS WITHDRAWN FROM THIS STUDY SINCE THE LAST IRB APPROVAL?
- ☒ No
- ☐ Yes (Discuss in the attached narrative)

CHANGE IN PRINCIPAL INVESTIGATOR:
- ☒ None
- ☐ Delete: _____
- ☐ Add: _____

HAVE ANY ASSOCIATE INVESTIGATORS BEEN ADDED OR DELETED SINCE LAST REVIEW?
- ☐ No
- ☐ Yes (Identify all changes in the attached narrative)

CHANGE IN MEDICAL ADVISORY INVESTIGATOR:
- ☒ None
- ☐ Delete: _____
- ☐ Add: _____

CHANGE IN RESEARCH CONTACT: ☐ No ☐ Yes

Trey Sunderland, M.D. 10/3N218
Name (Degree) Address
301-496-0948 301-435-6051 Trey@mail.nih.gov
Telephone FAX e-mail

INVESTIGATIONAL NEW DRUG/DEVICE:
- ☒ None ☐ IND ☐ IDE
- FDA No. _____
- Name _____
- Sponsor _____
- Holder _____

HAVE ANY NON-NIH INVESTIGATORS OR SITES BEEN ADDED SINCE THE LAST REVIEW?
- ☒ No
- ☐ Yes (Identify the persons or sites and describe the collaboration in the attached narrative)

IONIZING RADIATION USE (X-rays, radioisotopes, etc.):
- ☐ None
- ☒ Medically indicated only
- ☐ Research indicated:
  - ☐ Research usage HAS NOT changed since originally approved by the IRB and RSC
  - ☐ Research usage HAS changed since originally approved by the IRB and RSC (explain changes in the attached narrative)

HAVE ANY INVESTIGATORS DEVELOPED AN EQUITY OR CONSULTATIVE RELATIONSHIP WITH A NON-NIH SOURCE RELATED TO THIS PROTOCOL WHICH MIGHT BE CONSIDERED A CONFLICT OF INTEREST?
- ☒ No
- ☐ Yes (Append a statement of disclosure)

The Principal Investigator must attach to this application: (1) a copy of the current consent/assent documents and (2) a memorandum to the IRB Chairperson that addresses any "yes" responses to the above questions, and that includes a concise statement regarding protocol progress to date and reason(s) for continuing the study.

SIGNATURE Trey Sunderland	Principal Investigator	Date 1/7/04	Send to Accountable Investigator
RECOMMENDATION Trey Sunderland	Accountable Investigator	Date 1/7/04	Send to Branch Chief, or CC Department Head of Principal Investigator
D. Rubinow	Branch Chief, or CC Dept. Head of P.I.	Date 1/7/04	Send to Clinical Director
APPROVALS J.D. Rosenstein	Clinical Director	Date 2/11/04	Send to Chair, Institutional Review Board
	Chair, Institutional Review Board	Date 2/20/04	Send to Protocol Coordination Service Center, MRD (10/1N208) through IRB Protocol Coordinator
COMPLETION	Protocol Specialist	Date 3/24/04	Protocol and Consent Approved Effective

*U.S. GPO: 1999-454-653/00011

Clinical Research Protocol: Continuing Review Application
NIH-1195-1 (8-98)

Copy: Protocol Coordination Service Center

CLINICAL RESEARCH PROTOCOL: CONTINUING REVIEW APPLICATION

PROTOCOL NO.: 01-M-0128

PRINCIPAL INVESTIGATOR (Print or Type Name): TREY SUNDERLAND, MD

PROTOCOL TITLE: A Study of Immunomodulatory vs. Anti-inflammatory Therapy in Alzheimer's Disease

ACTION REQUESTED:
- ☑ Renew -New subject accrual to continue
- ☐ Renew -Enrolled subject followup only
- ☐ Terminate-Protocol discontinued (describe briefly in the attached narrative.)

HAVE THERE BEEN ANY AMENDMENTS SINCE THE LAST REVIEW?
- ☑ No
- ☐ Yes (Describe briefly in the attached narrative)

SUMMARY OF PROTOCOL SUBJECTS:
- 60 Accrual ceiling set by IRB
- 9 New subjects accrued since last review
- 15 Total subjects accrued since protocol began (If accrual has been less than expected, discuss in the attached narrative)

ACCRUAL EXCLUSIONS:
- ☑ None ☐ Male
- ☐ Female ☐ Other: _____

IMPAIRED SUBJECTS:
- ☐ None ☐ Physically ☑ Cognitively

HAVE THERE BEEN ANY CHANGES IN THE SUBJECT POPULATION, RECRUITMENT OR SELECTION CRITERIA SINCE THE LAST REVIEW?
- ☑ No
- ☐ Yes (Explain changes in the attached narrative)

HAVE THERE BEEN ANY CHANGES IN THE INFORMED CONSENT PROCESS OR DOCUMENTATION SINCE THE LAST REVIEW?
- ☑ No
- ☐ Yes (Explain changes in the attached narrative)

ANY INFORMATION APPEARED IN THE LITERATURE, OR EVOLVED THIS OR SIMILAR RESEARCH, THAT MIGHT AFFECT THE IRB's EVALUATION OF THE RISK/BENEFIT ANALYSIS OF HUMAN SUBJECTS INVOLVED IN THIS PROTOCOL?
- ☑ No
- ☐ Yes (Discuss in the attached narrative)

HAVE ANY UNEXPECTED COMPLICATIONS OR SIDE EFFECTS BEEN NOTED SINCE LAST REVIEW?
- ☑ No
- ☐ Yes (Identify and explain in attached narrative)

HAVE ANY SUBJECTS WITHDRAWN FROM THIS STUDY SINCE THE LAST IRB APPROVAL?
- ☑ No
- ☐ Yes (Discuss in the attached narrative)

CHANGE IN PRINCIPAL INVESTIGATOR:
- ☑ None
- ☐ Delete: _____
- ☐ Add: _____

HAVE ANY ASSOCIATE INVESTIGATORS BEEN ADDED OR DELETED SINCE LAST REVIEW?
- ☐ No
- ☑ Yes (Identify all changes in the attached narrative)

CHANGE IN MEDICAL ADVISORY INVESTIGATOR:
- ☑ None
- ☐ Delete: _____
- ☐ Add: _____

CHANGE IN RESEARCH CONTACT: ☑ No ☐ Yes

Name (Degree) Address

Telephone FAX e-mail

INVESTIGATIONAL NEW DRUG/DEVICE:
- ☑ None ☐ IND ☐ IDE
- FDA No. _____
- Name _____
- Sponsor _____
- Holder _____

HAVE ANY NON-NIH INVESTIGATORS OR SITES BEEN ADDED SINCE THE LAST REVIEW?
- ☑ No
- ☐ Yes (Identify the persons or sites and describe the collaboration in the attached narrative)

IONIZING RADIATION USE (X-rays, radioisotopes, etc.):
- ☐ None
- ☑ Medically indicated only
- ☐ Research indicated:
  - ☐ Research usage HAS NOT changed since originally approved by the IRB and RSC
  - ☐ Research usage HAS changed since originally approved by the IRB and RSC (explain changes in the attached narrative)

HAVE ANY INVESTIGATORS DEVELOPED AN EQUITY OR CONSULTATIVE RELATIONSHIP WITH A NON-NIH SOURCE RELATED TO THIS PROTOCOL WHICH MIGHT BE CONSIDERED A CONFLICT OF INTEREST?
- ☑ No
- ☐ Yes (Append a statement of disclosure)

The Principal Investigator must attach to this application: (1) a copy of the current consent/assent documents and (2) a memorandum to the IRB Chairperson that addresses any "yes" responses to the above questions, and that includes a concise statement regarding protocol progress to date and reason(s) for continuing the study.

SIGNATURE	Principal Investigator	Date 3/10/03	Send to Accountable Investigator
RECOMMENDATION	Accountable Investigator	Date 3/10/03	Send to Branch Chief, or CC Department Head of Principal Investigator
	Branch Chief, or CC Dept. Head of P.I.	Date 3/19/03	Send to Clinical Director
APPROVALS	Clinical Director	Date 4/24/03	Send to Chair, Institutional Review Board
	Chair, Institutional Review Board	Date 4/23/03 Protocol and Consent Approved Effective	Send to Protocol Coordination Service Center, MRD (10/1N208) through IRB Protocol Coordinator
COMPLETION	Protocol Specialist	Date 4-14-2003	

*U.S. GPO: 1999--454-653/00011

Clinical Research Protocol: Continuing Review Application
NIH-1195-1 (8-98)

Copy: Institute Protocol Coordinator

CLINICAL RESEARCH PROTOCOL: **CONTINUING** REVIEW APPLICATION	PROTOCOL NO. 01-M-0128	PRINCIPAL INVESTIGATOR (Print or Type Name): Trey Sunderland, M.D.

PROTOCOL TITLE:
Pilot Study of Immunomodulatory versus Antiinflammatory Therapy in Alzheimer's Disease

ACTION REQUESTED:
- ☑ Renew -New subject accrual to continue
- ☐ Renew -Enrolled subject followup only
- ☐ Terminate-Protocol discontinued (describe briefly in the attached narrative.)

HAVE THERE BEEN ANY AMENDMENTS SINCE THE LAST REVIEW?
- ☐ No
- ☑ Yes (Describe briefly in the attached narrative)

SUMMARY OF PROTOCOL SUBJECTS:
- 60 Accrual ceiling set by IRB
- 6 New subjects accrued since last review
- 6 Total subjects accrued since protocol began (If accrual has been less than expected, discuss in the attached narrative)

ACCRUAL EXCLUSIONS:
- ☑ None ☐ Male
- ☐ Female ☐ Other: _____

IMPAIRED SUBJECTS:
- ☐ None ☐ Physically ☑ Cognitively

HAVE THERE BEEN ANY CHANGES IN THE SUBJECT POPULATION, RECRUITMENT OR SELECTION CRITERIA SINCE THE LAST REVIEW?
- ☑ No
- ☐ Yes (Explain changes in the attached narrative)

HAVE THERE BEEN ANY CHANGES IN THE INFORMED CONSENT PROCESS OR DOCUMENTATION SINCE THE LAST REVIEW?
- ☑ No
- ☐ Yes (Explain changes in the attached narrative)

...NY INFORMATION APPEARED IN THE LITERATURE, OR EVOLVED ...M THIS OR SIMILAR RESEARCH, THAT MIGHT AFFECT THE IRB's EVALUATION OF THE RISK/BENEFIT ANALYSIS OF HUMAN SUBJECTS INVOLVED IN THIS PROTOCOL?
- ☑ No
- ☐ Yes (Discuss in the attached narrative)

HAVE ANY UNEXPECTED COMPLICATIONS OR SIDE EFFECTS BEEN NOTED SINCE LAST REVIEW?
- ☑ No
- ☐ Yes (Identify and explain in attached narrative)

HAVE ANY SUBJECTS WITHDRAWN FROM THIS STUDY SINCE THE LAST IRB APPROVAL?
- ☑ No
- ☐ Yes (Discuss in the attached narrative)

CHANGE IN PRINCIPAL INVESTIGATOR:
- ☑ None
- ☐ Delete: _____
- ☐ Add: _____

HAVE ANY ASSOCIATE INVESTIGATORS BEEN ADDED OR DELETED SINCE LAST REVIEW?
- ☑ No
- ☐ Yes (Identify all changes in the attached narrative)

CHANGE IN MEDICAL ADVISORY INVESTIGATOR:
- ☑ None
- ☐ Delete: _____
- ☐ Add: _____

CHANGE IN RESEARCH CONTACT: ☐ No ☐ Yes

Name (Degree) Address

Telephone FAX e-mail

INVESTIGATIONAL NEW DRUG/DEVICE:
- ☑ None ☐ IND ☐ IDE
- FDA No. _____
- Name _____
- Sponsor _____
- Holder _____

HAVE ANY NON-NIH INVESTIGATORS OR SITES BEEN ADDED SINCE THE LAST REVIEW?
- ☑ No
- ☐ Yes (Identify the persons or sites and describe the collaboration in the attached narrative)

IONIZING RADIATION USE (X-rays, radioisotopes, etc.):
- ☐ None
- ☑ Medically indicated only
- ☐ Research indicated:
  - ☐ Research usage HAS NOT changed since originally approved by the IRB and RSC
  - ☐ Research usage HAS changed since originally approved by the IRB and RSC (explain changes in the attached narrative)

HAVE ANY INVESTIGATORS DEVELOPED AN EQUITY OR CONSULTATIVE RELATIONSHIP WITH A NON-NIH SOURCE RELATED TO THIS PROTOCOL WHICH MIGHT BE CONSIDERED A CONFLICT OF INTEREST?
- ☑ No
- ☐ Yes (Append a statement of disclosure)

The Principal Investigator must attach to this application: (1) a copy of the current consent/assent documents and (2) a memorandum to the IRB Chairperson that addresses any "yes" responses to the above questions, and that includes a concise statement regarding protocol progress to date and reason(s) for continuing the study.

SIGNATURE	Principal Investigator — Date 2/22/02		Send to Accountable Investigator
RECOMMENDATION	Accountable Investigator — Date 2/22/02		Send to Branch Chief, or CC Department Head of Principal Investigator
	Branch Chief, or CC Dept Head of P.I. — Date 2/22/02		Send to Clinical Director
APPROVALS	Clinical Director — Date 4/19/02		Send to Chair, Institutional Review Board
	Chair, Institutional Review Board — Date 4/23/02	Protocol and Consent Approved Effective	Send to Protocol Coordination Service Center, MRD (10/1N208) through IRB Protocol Coordinator
COMPLETION	Protocol Specialist — Date	4/26/02	

CLINICAL RESEARCH PROTOCOL: **ONTINUING** REVIEW APPLICATION	PROTOCOL NO. 02-M-0305	PRINCIPAL INVESTIGATOR (Print or Type Name): TREY SUNDERLAND, MD

PROTOCOL TITLE: THE EFFECT OF SHORT TERM STATIN + NSAID TREATMENT ON CSF β-AMYLOID

ACTION REQUESTED:
- [X] Renew -New subject accrual to continue
- [ ] Renew -Enrolled subject followup only
- [ ] Terminate-Protocol discontinued (describe briefly in the attached narrative.)

HAVE THERE BEEN ANY AMENDMENTS SINCE THE LAST REVIEW?
- [X] No
- [ ] Yes (Describe briefly in the attached narrative)

SUMMARY OF PROTOCOL SUBJECTS:
- 50 Accrual ceiling set by IRB
- 22 New subjects accrued since last review
- 22 Total subjects accrued since protocol began (If accrual has been less than expected, discuss in the attached narrative)

ACCRUAL EXCLUSIONS:
- [X] None [ ] Male
- [ ] Female [ ] Other: _____

IMPAIRED SUBJECTS:
- [X] None [ ] Physically [ ] Cognitively

HAVE THERE BEEN ANY CHANGES IN THE SUBJECT POPULATION, RECRUITMENT OR SELECTION CRITERIA SINCE THE LAST REVIEW?
- [X] No
- [ ] Yes (Explain changes in the attached narrative)

HAVE THERE BEEN ANY CHANGES IN THE INFORMED CONSENT PROCESS OR DOCUMENTATION SINCE THE LAST REVIEW?
- [X] No
- [ ] Yes (Explain changes in the attached narrative)

AS ANY INFORMATION APPEARED IN THE LITERATURE, OR EVOLVED FROM THIS OR SIMILAR RESEARCH, THAT MIGHT AFFECT THE IRB's EVALUATION OF THE RISK/BENEFIT ANALYSIS OF HUMAN SUBJECTS INVOLVED IN THIS PROTOCOL?
- [X] No
- [ ] Yes (Discuss in the attached narrative)

HAVE ANY UNEXPECTED COMPLICATIONS OR SIDE EFFECTS BEEN NOTED SINCE LAST REVIEW?
- [X] No
- [ ] Yes (Identify and explain in attached narrative)

HAVE ANY SUBJECTS WITHDRAWN FROM THIS STUDY SINCE THE LAST IRB APPROVAL?
- [X] No
- [ ] Yes (Discuss in the attached narrative)

CHANGE IN PRINCIPAL INVESTIGATOR:
- [X] None
- [ ] Delete: _____
- [ ] Add: _____

HAVE ANY ASSOCIATE INVESTIGATORS BEEN ADDED OR DELETED SINCE LAST REVIEW?
- [ ] No
- [X] Yes (Identify all changes in the attached narrative)

CHANGE IN MEDICAL ADVISORY INVESTIGATOR:
- [X] None
- [ ] Delete: _____
- [ ] Add: _____

CHANGE IN RESEARCH CONTACT: [X] No [ ] Yes

Name (Degree) _____ Address _____

Telephone _____ FAX _____ e-mail _____

INVESTIGATIONAL NEW DRUG/DEVICE:
- [X] None [ ] IND [ ] IDE
- FDA No. _____
- Name _____
- Sponsor _____
- Holder _____

HAVE ANY NON-NIH INVESTIGATORS OR SITES BEEN ADDED SINCE THE LAST REVIEW?
- [X] No
- [ ] Yes (Identify the persons or sites and describe the collaboration in the attached narrative)

IONIZING RADIATION USE (X-rays, radioisotopes, etc.):
- [X] None
- [ ] Medically indicated only
- [ ] Research indicated:
  - [ ] Research usage HAS NOT changed since originally approved by the IRB and RSC
  - [ ] Research usage HAS changed since originally approved by the IRB and RSC (explain changes in the attached narrative)

HAVE ANY INVESTIGATORS DEVELOPED AN EQUITY OR CONSULTATIVE RELATIONSHIP WITH A NON-NIH SOURCE RELATED TO THIS PROTOCOL WHICH MIGHT BE CONSIDERED A CONFLICT OF INTEREST?
- [X] No
- [ ] Yes (Append a statement of disclosure)

The Principal Investigator must attach to this application: (1) a copy of the current consent/assent documents and (2) a memorandum to the IRB Chairperson that addresses any "yes" responses to the above questions, and that includes a concise statement regarding protocol progress to date and reason(s) for continuing the study.

SIGNATURE	Robert M. Cohen, MD for Trey Sunderland, MD (Principal Investigator)	Date	8/04/03	Send to Accountable Investigator
RECOMMENDATION	Robert M. Cohen, MD for Trey Sunderland, MD (Accountable Investigator)	Date	8/04/03	Send to Branch Chief, or CC Department Head of Principal Investigator
	Robert M. Cohen, MD for Trey Sunderland (Branch Chief, or CC Dept. Head of P.I.)	Date	8/04/03	Send to Clinical Director
APPROVALS	(Clinical Director)	Date	9/4/03	Send to Chair, Institutional Review Board
	(Chair, Institutional Review Board)	Date	9/15/03	Send to Office of Protocol Services, MRD (10/1N208) through IRB Protocol Coordinator
COMPLETION	(Protocol Specialist)	Date	Protocol and Consent Approved Effective 10/08/03	

Tab 25

To: Trey Sunderland, David Rubinow
From: Karen T Putnam
Subject: GPB Pfizer Assay samples

We have sent CSF samples to Pfizer from 538 subjects from GPB/NIMH. The dates of these samples go back to 1983. Of those 538 subjects, 25 were blinded vials of young schizophrenics from Judy Rapoport's branch. The assays done were for beta-amyloid $_{1\text{-}42}$, beta-amyloid $_{1\text{-}40}$ and tau.

DIAG	Frequency	Cumulative Frequency
AD	200	200
CNL	302	502
OTH	11	513
YSC	25	538

For the 538 subjects, the data was initially collected on subjects during an evaluation period prior to entering any drug protocol. For those subjects that we have obtained Pfizer assay data- 94% were samples are clearly during the evaluation period. It wasn't unusual for the baseline evaluation CSF to be depleted from our freezers for other uses prior to any assay shipments to Pfizer. Additionally, we have had a couple of freezer breakdowns that have resulted in having to depose of thawed sampled.

Multiple samples have been sent from these 538 subjects; both from different taps dates (longitudinal data) and repeat samples from the same date for QC. The total number of samples sent to Pfizer equals 2132 vials for beta-amyloid $_{1\text{-}42}$, beta-amyloid $_{1\text{-}40}$ and tau. The GPB primary protocols that have been pulled for these assays are BIOCARD 95-M-96 (46%) and an older protocol for yearly AD & Control longitudinal drug free follow-up 82-M-123 (23%). The current GPB protocol Cyclophosphamide #01-M-128 accounts of 6% of the CSF samples. The remaining 25% are from past GPB protocols ranging from a drug free bereavement study to some acute drug studies. Typically GPB drug studies included a placebo phase.

The data included here is still being checked and should be considered DRAFT.
20JUN2005

Karen T Putnam

Tab 26

Subject: GPB/Pfizer Collaboration

Coded CSF samples have been sent to Pfizer from 538 subjects from GPB/NIMH through the NIH-approved MTA. Of those 538 subjects, 513 came from the GPB and 25 were blinded samples from young schizophrenic patients from Judy Rapoport's branch. The assays were performed in a blinded fashion and included β-amyloid$_{1-42}$, β-amyloid$_{1-40}$ and tau.

It should be noted that this scientific collaboration between the GPB and Pfizer was one of 25-30 collaborative projects that have been conducted by the GPB with these same subjects and other CSF samples over the last 22 years in conjunction with various academic and industry scientists.

DIAGNOSIS	Number of Subjects	Cumulative Frequency
Dementia (eg. Alzheimer's)	211	211
Control Subjects	302	513
Schizophrenic patients	25	538

Protocol Numbers and Percent of Total Subjects (%) for the CSF study:

95-M-0096 (50%)
82-M-0123 (34%)
78-M-0148 & 95-M-0025 (5%)
The remaining 11% of the subjects came in small numbers from numerous studies dating back to the 1980's (85-M-0207, 88-M-0008, 88-M-0009, 88-M-0076, 88-M-0126, 91-M-0194, 97-M-0157, 01-M-0128 & 02-M-0305).

Feb-15-2006 06:50pm From-Assistant Secretary for Legislation 202-690-7380 T-118 P.002 F-213
02/14/2006 11:27 FAX 301 480 2381 001

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

National Institutes of Health
Bethesda, Maryland 20892
www.nih.gov

May 10, 2005

TO: Colleen Barros
Deputy Director for Management, NIH

FROM: Director, NIH Ethics Office

SUBJECT: Karen Putnam's Unapproved Outside Activity with Pfizer

The NIH Ethics Review Panel examined an unapproved outside consulting activity between Pfizer and Karen Putnam, Research Assistant, Geriatric Psychiatry Branch, National Institute of Mental Health (NIMH). The Panel finds a significant overlap between the scientific subject matter of the consulting activity with Pfizer and Ms. Putnam's official duties.

Between January 2001 and June 2004, Karen Putnam served as a consultant for Pfizer and was involved in projects related to the study of its Alzheimer's drug Aricept. Ms. Putnam entered into a consulting agreement with Pfizer to advise the company on statistics and data management for studies investigating "biomarkers for neurological disease." She worked specifically with Pfizer statisticians and researchers to evaluate the statistical results and the methods applied to distinguish between healthy controls and Alzheimer's patients and to evaluate the company's data on the rates of progression in Alzheimer's disease.

At NIMH, Ms. Putnam's official duties include statistical analysis and data management for the Geriatric Psychiatry Branch (GPB), which focuses on the study of biomarkers for Alzheimer's disease. She works to ensure the integrity of GPB data, applying appropriate statistical analyses to data that captures a range of information from GPB studies on Alzheimer's disease.

Even though Ms. Putnam does not work in drug testing nor with any Pfizer drugs, the Ethics Review Panel finds that the scientific subject matter of her unapproved outside activity with Pfizer is too close to her official responsibilities at NIMH. The Panel finds that she works in the same scientific area, which deals directly with the study of biomarkers for Alzheimer's disease, and that the research problems that she faces in her position at NIMH are very similar to the work that she did for Pfizer, which was to advise the company on its statistical methodology for the study of biomarkers for Alzheimer's disease. Accordingly, the Panel concludes that Ms. Putnam would not have received approval for the activity, if she had sought it, because her official duties overlap with the scientific subject matter of the consultancy with Pfizer.

Holli Beckerman Jaffe, J.D.

cc: Suzanne Servis, OMA

Tab 27

COLLABORATIVE RESEARCH AGREEMENT

Whereas, Abbott Laboratories, located at Abbott Park, Illinois, 60064 (hereinafter "Abbott") and the National Institute of Mental Health, Division of Intramural Research, Laboratory of Clinical Science, Bethesda, Md. 20892 (hereinafter "NIMH"), a component agency of the Department of Health and Human Services (hereinafter "DHHS"), desire to enter into an Agreement to collaborate in research;

Whereas, Abbott has acquired certain rights regarding ALZ 50, a protein found in human brain, having potential usefulness in the diagnosis of Alzheimer's disease; and

Whereas, NIMH has access to a large pool of human patients with probable Alzheimer's disease,

NOW THEREFORE, for and in consideration of the following mutual covenants, the parties to this Agreement agree as follows:

1. Purpose

The purpose of this study is to evaluate the usefulness of ALZ 50 as a diagnostic test for Alzheimer's disease. Samples of cerebrospinal fluid (CSF) collected by NIMH from patients with probable Alzheimer's disease, normal controls, and elderly depressed patients not believed to have Alzheimer's disease, will be provided to Abbott for analysis and evaluation of the presence of ALZ 50.

2. Definitions

a. "Protocol" means the procedure set forth in Exhibit A, attached hereto and incorporated into this Agreement by reference.

b. "Study" means an investigation conducted during the period specified below by NIMH and Abbott related to ALZ 50 in accordance with the Protocol or any amendments or modifications thereto.

c. "Proprietary Information" means information of Abbott which embodies trade secrets or confidential business or financial information, excluding such information which:

i. is already known to NIMH at the time of disclosure;

ii. is generally known or available from other sources without obligations concerning its confidentiality;

iii. has been made available by Abbott to others without obligation concerning its confidentiality; or

iv. is or becomes publicly known through no fault of NIMH.

CONFIDENTIAL

Tab 28

c. "Data" means any and all data, including raw data, syntheses, abstracts, reports, statistical analyses, laboratory analyses and the like which are prepared or obtained by NIMH during the course of and/or at completion of the Study.

e. "Patent Rights" means the world-wide rights under any and all patents relating to the Study covering inventions made during the period of the Study.

f. "Inventions" means any invention or discovery which is or may be patentable or otherwise protected under Title 35, United States Code.

3. Principal Investigator

The collaborator for the NIMH portion of the Study is Dr. Trey Sunderland, who is personally responsible for conducting the Study. The principal collaborator for the Abbott portion of the Study is Henry L. Haigler. In the event Dr. Sunderland becomes unable to complete the Study for any reason, Abbott and NIMH may mutually agree to a substitute principal collaborator, in which event this Agreement shall continue in full force and effect. If Abbott and NIMH cannot agree on a substitute, the Study shall immediately terminate upon request of one party to the other, without liability to either party.

4. Financial

Abbott shall pay NIMH $50 per CSF specimen during the first year of the study and a mutually agreed upon amount for any subsequent year. Abbott shall reimburse NIMH for all reasonable expenses incurred with respect to the handling, storage, and shipping of CSF specimens during the Study.

5. Nondisclosure and Nonuse Obligations

Abbott shall designate as "Confidential, Property of Abbott Laboratories," information it delivers to NIMH under this Agreement which it considers to be Proprietary Information. Subject to Paragraph 7 and subparagraph 5(a) below, NIMH will not disclose any Proprietary Information received from Abbott to third parties, or to other NIMH personnel who do not have a need to know for purposes of the Study, without the prior written consent of Abbott. Furthermore, NIMH will not use the Proprietary Information disclosed to it by Abbott other than for the purpose of conducting the Study.

a. If information is requested under the Freedom of Information Act, 5 U.S.C. § 552, NIMH shall use its best efforts to protect information designated by Abbott as Proprietary Information from unauthorized disclosure. NIMH shall not be liable for the disclosure of information designated as Proprietary Information which, after notice to and consultation with Abbott, NIMH determines may not lawfully be withheld or which a court of competent jurisdiction requires to be disclosed. Abbott shall be free to challenge any final agency determination that the Proprietary Information is not exempt from disclosure under the Freedom of Information Act.

CONFIDENTIAL

Abbott upon completion of the Study except that NIMH may keep one copy of any Proprietary Information in written form for archival purposes. The nondisclosure and nonuse obligations of NIMH under this section will continue for a period of ten (10) years after the termination of this Agreement.

6. Reports

NIMH shall provide Abbott with written copies of all laboratory methods and procedures used in the categorization and collection of specimens provided to Abbott under this Study. NIMH shall also consult with Charles Nemeroff, M.D. Ph.D, of Duke University Medical Center or whomever Abbott may designate on issues regarding diagnostics, patient selection criteria, specimen collection, and handling and storage procedures. Such consultation may occur during meetings at mutually agreed upon times and locations, not to exceed one (1) day per month. When such consultation takes place outside Bethesda or at a professional meeting, Abbott shall reimburse NIMH for reasonable travel expenses which are incurred at the prior request, and with the prior approval, of Abbott.

7. Rights in Data; Publication of Results

a. Subject to the provisions of Paragraph 5, NIMH shall have the right to publish the results of this Study. NIMH shall provide Abbott with a copy of any proposed manuscript for review prior to submission for publication. Abbott shall have ninety (90) days after receipt of such proposed manuscript to (a) designate any information that is Proprietary Information and should be deleted; and (b) designate any information which Abbott intends to utilize to prepare and file a patent application. For purposes of publication of the Study, Proprietary Information shall not include data prepared or obtained by NIMH during the course or completion of the Study.

b. In the event Abbott notifies NIMH pursuant to subparagraph 7(a) above of information which Abbott intends to utilize for the preparation and filing of a patent application, Abbott shall then have ninety (90) days after notice to NIMH to prepare and file such patent application. NIMH shall not transfer the information to third parties, including in any manuscript for publication, or have the same published before expiration of the ninety (90) day period. Abbott shall not be permitted to prevent the transfer of information to third parties or publication except to the extent provided above.

8. Patent Rights

a. All patent rights to any invention made by personnel of Abbott or its affiliates prior to execution to this Agreement or independently of this Agreement such as, but not limited to, those personnel who did not have access to or knowledge or information from the Study, with respect to ALZ 50, shall belong to Abbott. In no event shall this Agreement be deemed to diminish Abbott's established patent rights (including background patent rights) relating to ALZ 50.

b. All inventions and discoveries (whether or not patentable) which result from the

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Study wherein:

i. one or more agents or employees of NIMH, only, are inventors, shall be solely owned by DHHS;

ii. one or more agents or employees of Abbott, only, are inventors, shall be solely owned by Abbott;

iii. one or more agents or employees of NIMH are joint inventors with one or more agents or employees of Abbott, shall be jointly owned by DHHS and Abbott.

9. Licenses

DHHS does hereby grant to Abbott a non-exclusive, royalty-bearing license under patent rights owned by DHHS under this Agreement. Upon written notice to DHHS by Abbott, the parties shall negotiate in good faith and within a reasonable time the non-exclusive license under the Patent Rights. The license granted herein will be issued on behalf of the United States Government by the National Technical Information Services who will represent DHHS in licensing negotiations. The royalty rate shall be not more than 10 percent of the annual gross commercial sales of products encompassed by the Patent Rights.

10. Preparation, Filing and Maintenance of Patent Rights

As to any of the Patent Rights owned by DHHS under this Agreement, either wholly or jointly, Abbott and/or Abbott's foreign affiliates, at their sole option, shall have the right on behalf of DHHS or NIMH to prepare, file and prosecute patent applications in the United States and world wide covering such Patent Rights and pay maintenance fees for any patent applications or patents issuing thereon at Abbott's expense. Abbott shall promptly provide to the DHHS Patent Branch copies of all patent applications and all communications received from or filed in the United States Patent and Trademark Office in connection with such patent applications, filed on inventions developed pursuant to this Agreement which name as an inventor or co-inventor any person who is employed by or is under the control of NIMH or DHHS and is working on the Study whose patent rights are subject to disposition in accordance with the provisions of Executive Order 10096. Abbott shall, upon request, provide to the DHHS Patent Branch, Powers of Attorney, authorizing the Chief of the Patent Branch or his/her designee to examine and make copies of the contents of the Patent Office file wrapper of such patent applications. If Abbott, including its foreign affiliates, should refuse to undertake at DHHS's or NIMH's request the preparation, filing or prosecution of any patent application covering the above-referenced Patent Rights or to pay maintenance fees on any patents or patent applications, DHHS or NIMH may do so on its own and at its own expense.

11. Duration and Termination of Agreement

This Agreement shall be effective for a period of one (1) year following the date of acceptance below, and may be extended upon written agreement of Abbott and NIMH.

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days after service of written notice of termination upon one party by the other. All rights and obligations of the parties acquired prior to termination of this Agreement shall survive termination of the Agreement.

12. Applicable Law

This agreement shall be governed by the laws of the United States and the State of Illinois. In case of conflict, the laws of the United States shall govern.

13. Notice

Whenever any notice is to be given under the terms of this Agreement, it shall be in writing and mailed to then following addresses by registered or certified mail receipt requested:

NIMH: Dr. Trey Sunderland
National Institute of Mental Health
Division of Intramural Research Laboratory of Clinical Science
Bldg. 10 Room 3D41
Bethesda, Maryland 20892

Abbott: Director of Technology Assessment and Acquisition
Department 9RK, AP6C
Abbott Laboratories
Abbott Park, Illinois 60064

cc: Office of General Counsel
Abbott Laboratories
Abbott Park, Illinois 60064

14. No Waiver

No failure to exercise any right or demand performance of any obligation under this Agreement shall be deemed a waiver of such right or obligation except as expressly provided.

15. Entire Agreement

This Agreement represents the entire understanding of the parties with respect to the subject matter thereof. Any modification or renewal of this Agreement shall be made in writing and must be signed by both parties.

16. Assignment

This Agreement may not be assigned by either party without the prior written consent of the other party.

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No indemnification is intended or provided under this Agreement. Each party shall. be individually responsible for any liability which it incurs as a result of its activities under this Agreement.

18. Use Of Name

Abbott shall not use the name of the NIMH, DHHS, or the Federal government, or its participation in this study for promotional purposes. Any proposed reference to NIMH, DHHS, or the Federal government in an Abbott publication involving the Study must have prior written approval by NIMH. Similarly, NIMH agrees not to use the name of Abbott in any publicity or advertising without Abbott's prior written approval.

19. Disputes

In the event of any dispute between Abbott and NIMH arising out of this Agreement which cannot be settled by discussion and consultation between the parties, such dispute shall be referred to the Administrator, ADAMHA, or his/her designate and then to the Assistant Secretary for Health, DHHS, or his/her designate, for resolution.

20. Miscellaneous

This Agreement does not form any partnership or joint venture between Abbott and NIMH. The terms of this agreement are not inconsistent with the policies of NIMH, including, but not limited to, policies regarding the administration of grants and funded research.

AGREED AND ACCEPTED:

For the U.S. Government

5/18/89

Lewis L. Judd, M.D. Date
Director, National Institute of Mental Health

For Abbott:

6-27-89

Signature Date

Name: David V. Milligan

Title: V.P. - Div Prod R+D

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Exhibit A

Study/Protocol Involving ALZ 50

A. NIMH shall provide to Abbott at a location designated by Abbott, approximately 115 human CSF specimens, obtained from patients with DSM-III primary degenerative dementia/NINCDS (probable Alzheimer's disease), normal controls, or elderly depressed patients, as set forth in the project protocol which will be submitted to NIMH in writing by Henry J. Haigler, Ph.D., or his designee, on behalf of Abbott. NIMH will assure that all CSF specimens will be properly categorized, characterized and traceable to well-documented patient records. The samples will be broken into two groups, A-unblinded, B-blinded. Group A will include CSF from 5 controls, 10 depressed patients and 35 from patients with Alzheimer's disease. The second group B, will consist of 65 CSF samples. NIMH will code these 65 CSF specimens and send them to Abbott without any diagnosis so that the analysis can be carried out on blind basis.

B. At the completion of the second half of the Study, NIMH will provide Abbott with the previously coded information on the categorization and characterization of all CSF specimens provided during the Study and the case synopsis of each patient. NIMH will also provide Abbott with post-mortem reports on patients as available. Abbott shall provide NIMH with the results of any analysis and evaluation performed by Abbott on the CSF specimens provided by NIMH.

C. NIMH shall arrange for appropriate packaging, shipping conditions, and shipment of CSF specimens to Abbott, and shall provide follow-up specimens as deemed appropriate by Abbott to verify the accuracy of any test Abbott performs on any contributed specimen.

D. NIMH shall obtain the CSF specimens in accordance with 45 C.F R. Part 46, including obtaining the consent of each patient for use of the CSF specimens for research purposes.

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Tab 29

FORM PTO-1595
(Rev. 6/93)
8-22-01

08-27-2001
101823284

U.S. DEPARTMENT OF COMMERCE
Patent and Trademark Office

SHEET

Attorney Docket No. 2572-1-001N2

To the Assistant Commissioner for Patents

1. Name of conveying party(ies):

L. Kathryn Durham; David L. Friedman; Lida H. Kimmel; David M. Potter; B. Michael Silber; Thomas R. Stiger; P. Trey Sunderland; W. Frost White; Stephen A. Williams

Additional name(s) of conveying party(ies) attached? [ ] Yes [X] No

3. Nature of conveyance:

[X] Assignment (IN 2 COUNTERPARTS)
[ ] Security Agreement [ ] Change of Name

Other:

Execution Date: 6/20/01; 6/20/01; 6/20/01; 6/20/01; 6/20/01; 6/20/01; 7/1/01; 6/20/01; 6/20/01

2. Name and address of receiving party(ies):

Name: Pfizer Inc.

Address: 234 East 42nd Street

New York, New York 10017

Additional name(s) & address(es) attached? [ ] Yes [X] No

4. Application number(s) or patent number(s):

If this document is being filed together with a new application, the execution date of the application is:

A. Patent Application No.(s)
09/826,290

B. Patent No.(s)

Additional numbers attached? [ ] Yes [X] No

5. Name and address of party to whom correspondence concerning document should be mailed:

Name: DAVID A. JACKSON

Address: KLAUBER & JACKSON

411 Hackensack Avenue, 4th Floor

Hackensack, New Jersey 07601

6. Total number of applications and patents involved: 1

7. Total fee (37 CFR 3.41): $40.00

[X] Enclosed

[ ] Authorized to be charged to deposit account, if necessary - for overages or underpayments only

8. Deposit account number:

11-1153

(Attach duplicate copy of this page if paying by deposit account)

DO NOT USE THIS SPACE

9. Statement and signature.
To the best of my knowledge and belief, the foregoing information is true and correct and any attached copy is a true copy of the original document.

David A. Jackson, Reg. No. 26,742
Name of Person Signing

Signature

8/22/2001
Date

Total number of pages including cover sheet, attachments, and document: 2

Mail documents to be recorded with required cover sheet information to:

Assistant Commissioner for Patents
Box Assignments
Washington, D.C. 20231

08/24/2001 AHNEDI 00000190 09826290
01 FC:581 40.00 OP

(BDSM 8)
(9/94)

Attorney Docket No. 2572-1-001N2

ASSIGNMENT

LXD 6/20/2001

WHEREAS, We, L. **Kathryn K. Durham**, a citizen of the United States, residing at
94 Glenwood Avenue
New London, Connecticut 06320;

David L. Friedman, a citizen of the United States, residing at
368 Bartlett Drive
Madison, Connecticut 06443;

Lida H. Kimmel, a citizen of the United States, residing at
55 Bokum Road
Chester, Connecticut 06412;

David M. Potter, a citizen of the United States, residing at
33 Chriswood Trace
Ledyard, Connecticut 06339;

B. Michael Silber, a citizen of the United States, residing at
104 Randi Drive
Madison, Connecticut 06443;

Thomas R. Stiger, a citizen of the United States, residing at
93 Castle Hill Road
Pawcatuck, Connecticut 06379;

P. Trey Sunderland, a citizen of the United States, residing at
4718 Cumberland Avenue
Chevy Chase, Maryland 20815;

W. **Frost White**, a citizen of the United States, residing at
WFW 6/20/01 65 Homestead Road
Ledyard, Connecticut 06339; and

Stephen A. Williams, a citizen of Great Britain, residing at
114 Colony Road
Groton, Connecticut 06340,

ASSIGNORS, have invented new and useful improvements in

NUCLEIC ACID MOLECULES, POLYPEPTIDES AND USES THEREFORE, INCLUDING DIAGNOSIS AND TREATMENT OF ALZHEIMER'S DISEASE

PATENT
REEL: 012094 FRAME: 0093

for which we have filed an Application for Letters Patent in the United States on April 3, 2001, and assigned U.S. Serial No. 09/826,290.

WHEREAS, **Pfizer Inc.**
organized and existing under the laws of the state of Delaware
having an office at
234 East 42nd Street
New York, New York 10017,

ASSIGNEE, is desirous of obtaining the entire right, title and interest in, to and under the said improvements and the said application;

NOW, THEREFORE, for other good and valuable consideration, the receipt of which is hereby acknowledged, we the said

ASSIGNORS

have sold, assigned, transferred and set over, and by these presents do hereby sell, assign, transfer and set over, to the said

ASSIGNEE

its successors, legal representatives and assigns, the entire right, title and interest in, to and under the said improvements, and the said application and all divisions, renewals and continuations thereof, and all Letters Patent of the United States which may be granted thereon and all reissues and extensions thereof, and all applications for Letters Patent which may hereafter be filed for said improvements in any country or countries foreign to the United States, including the right to claim priority under the terms of any appropriate International Convention based upon said application for Letters Patent of the United States, and all Letters Patent which may be granted for said improvements in any country or countries foreign to the United States and extensions, renewals and reissues thereof; and we hereby authorize and request the Commissioner of Patents and Trademarks of the United States and any official of any country or countries foreign to the United States, whose duty it is to issue patents on applications as aforesaid, to issue all Letters Patent for said improvements to the said

ASSIGNEE,

its successors, legal representatives and assigns, in accordance with the terms of this instrument.

AND WE HEREBY covenant that we have full right to convey the interest herein assigned in the manner hereinabove set forth, and that we have not executed, and will not execute, any agreement in conflict herewith.

AND WE HEREBY further covenant and agree that we will communicate to the said

ASSIGNEE,

its successors, legal representatives and assigns, any fact known to us respecting said improvements, and testify in any legal proceeding, sign all lawful papers, execute all divisions, continuing and reissue applications, make all rightful oaths and generally do everything possible to aid the said

ASSIGNEE,

its successors, legal representatives and assigns, to obtain and enforce proper Patent Protection for said improvements in the United States.

IN TESTIMONY WHEREOF, we hereunto set our hand and seal the day and year set opposite our signatures.

Date 6/20, 2001 L. Kathryn Durham L.S.
L. Kathryn L. Durham LKD 6/20/2001

Date 6/20, 2001 David L. Friedman L.S.
David L. Friedman

Date 6/20, 2001 Lida H. Kimmel L.S.
Lida H. Kimmel

Date 6/20, 2001 David M. Potter L.S.
David M. Potter

Date 6/20, 2001 B. Michael S. W L.S.
B. Michael Silber

Date _____, 2001 _____ L.S.
Thomas R. Stiger

Date 7/1/01, 2001 _____ L.S.
P. Trey Sunderland

Date _____, 2001 _____ L.S.
W. Frost White

Date _____, 2001 _____ L.S.
Stephen A. Williams

Date _____, 2001 XXXXXXXXXXXXXXXXXX L.S.
Robert R. Townsend

RECORDED: 08/22/2001

PATENT
REEL: 012094 FRAME: 0100

Tab 30

US PATENT & TRADEMARK OFFICE

PATENT APPLICATION FULL TEXT AND IMAGE DATABASE

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United States Patent Application ***20020164668***
Kind Code **A1**
Durham, L. Kathryn ; et al. **November 7, 2002**

Nucleic acid molecules, polypeptides and uses therefor, including diagnosis and treatment of alzheimer's disease

Abstract

The present invention provides methods and compositions for screening, diagnosis and prognosis of Alzheimer's disease, for monitoring the effectiveness of Alzheimer's disease treatment, and for drug development. Alzheimer's ;ase-Associated Features (AFs), detectable by two-dimensional electrophoresis of cerebrospinal fluid, serum or plasma are described. The invention further provides Alzheimer's Disease-Associated Protein Isoforms (APIs) detectable in cerebrospinal fluid, serum or plasma, preparations comprising isolated APIs, antibodies, pharmaceutical compositions, diagnostic and therapeutic methods, and kits comprising or based on the same.

Inventors: **Durham, L. Kathryn**; *(New London, CT)* ; **Friedman, David L.**; *(Madison, CT)* ; **Chandrasiri Herath, Herath Mudiyanselage Athula**; *(Abingdom, GB)* ; **Kimmel, Lida H.**; *(Chester, CT)* ; **Parekh, Rajesh Bhikhu**; *(New Wendlebury, GB)* ; **Potter, David M.**; *(Ledyard, CT)* ; **Rohlff, Christian**; *(Oxford, GB)* ; **Silber, B. Michael**; *(Madison, CT)* ; **Stiger, Thomas R.**; *(Pawcatuck, CT)* ; **Sunderland, P. Trey**; *(Chevy Chase, MD)* ; **Townsend, Robert Reid**; *(Oxford, GB)* ; **White, W. Frost**; *(Ledyard, CT)* ; **Williams, Stephen A.**; *(Groton, CT)*

Correspondence Name and Address: **KLAUBER & JACKSON**
411 Hackensack Avenue
Hackensack
NJ
07601
US

Serial No.: **826290**
Series Code: **09**
Filed: **April 3, 2001**

.S. Current Class: 435/7.92; 435/226; 435/325; 435/69.1; 536/23.2
U.S. Class at Publication: 435/7.92; 435/69.1; 435/325; 435/226; 536/23.2

Tab 31

cc:Mail for: kathryn e monaghan

Subject: Re[3]: MTA for samples
From: B Michael Silber at CR_GROTON_NONCLIN25 3/24/98 4:39 PM
To: Kathryn E Monaghan at CR_GROTON_NONCLIN12

Kathy,

Thanks. OK with me to send out mesage. Absolutely! Please add my name to that message.

Thanks,

Michael

_____ Reply Separator _____
Subject: Re[2]: MTA for samples
Author: Kathryn E Monaghan at cr_groton_nonclin12
Date: 3/24/98 3:36 PM

Michael,

CRADA would be seperate from MTA and we could handle that - Josh and I have discussed this and we can deal with it either way to get some funds into NIH hands (since material comes without any $ cost to us).

Kathy

p.s. I thought I'd send a note out to the steering group later this week that OGS is signed and thanking everyone for all their hard work, effort - OK by you?

Subject: Re: MTA for samples
From: B Michael Silber at CR_GROTON_NONCLIN25
Date: 3/24/98 3:31 PM

Kathy,

Great to see we are getting closer. Are Trey/NIH still trying to get us to go CRADA? I thought you were able to head him "off at the pass."

Michael

_____ Reply Separator _____
Subject: MTA for samples
Author: Kathryn E Monaghan at cr_groton_nonclin12
Date: 3/24/98 3:16 PM

Trey,

I spoke with Kathy Conn today and she reconfirmed that we can proceed with the MTA immediately and work out the CRADA vs. Consult part in due course. I fedexed various forms of the MTA on Friday - hope you got them yesterday?

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NOT FOR PUBLIC DISCLOSURE/FOIA EXEMPT

Tab 32

Summary of the Office of Management Assessment's (OMA) Report on Dr. Trey Sunderland's Outside Activity Discrepancies

Factual Data:

The OMA's review of discrepancies between records provided by NIH and by Pfizer Inc. to the U.S. House of Representatives, Committee on Energy and Commerce, Subcommittee on Oversight Investigations, found that Dr. Sunderland:

A. Failed to Seek Prior Approval for Lectures, Honoraria and other Outside Consulting Activities, in Violation of Commissioned Corps Personnel Manual Chapter CC26 and the Code of Federal Regulations, 5 CFR 2635.02, and the NIH Manual Chapter 2300-735-4

1) Pfizer cited 140 dates in 1999-2004 when Dr. Sunderland gave lectures and received honoraria totaling $248,000. Dr. Sunderland cited 82 dates. Only 43 dates matched both lists. Dr. Sunderland did not obtain approval for any of these activities.

2) Pfizer reported consulting on 12 specific days. Dr. Sunderland's estimated list reports 25 dates. Only seven dates matched. Dr. Sunderland did not obtain approval for any of these activities.

3) After the NIH Director requested that scientists disclose any unreported outside activities with pharmaceutical or biotechnology companies, Dr. Sunderland reported consultations and lectures with 14 additional companies. Dr. Sunderland did not obtain approval for any of these activities.

B. Failed to disclose compensation he received from Pfizer and other companies on his OGE Form 450, *Executive Branch Confidential Disclosure* Reports from 1999-2003[1]

1) Pfizer cited that Dr. Sunderland was paid $248,000 in honoraria and lectures from 1999-2004. Dr. Sunderland did not report these earnings on his OGE 450 forms from 1999-2003.

2) Pfizer cited total payments of $228,500 to Dr. Sunderland for consulting services from 1999-2004. Dr. Sunderland did not report these monetary earnings on his OGE 450 forms from 1999-2003.

[1] OMA received different totals for payments to Dr. Sunderland for his outside activities from the Committee, Pfizer and Dr. Sunderland.

3) Dr. Sunderland reported consultations with monetary payments totaling $193,880 after being asked by the NIH Director to disclose unreported activities. Dr. Sunderland did not report these monetary earnings on his OGE 450 forms from 1999-2003.

C. Failed to Obtain Prior Approval for Outside Consulting Activities in Violation of Commissioned Corps Handbook, Section C.12.c, Use of Leave in Connection with Outside Activities

OMA determined that Dr. Sunderland was not on approved leave at least 34 days when he was engaging in outside activity. OMA notes that these numbers are likely higher but they were unable to verify specific additional activity dates.

D. Failed to Submit an OGE Form 278, *"Executive Branch Personnel Public Financial Disclosure Form"* for 2004

Dr. Sunderland has failed to submit his SF-278 Public Financial Disclosure Form for 2004. Despite being given several opportunities to complete the form, and the fact that his attorney was given specific information regarding why he was required to complete his SF-278 Public Financial Disclosure Form for 2004, as of this date, Dr. Sunderland still has not submitted the form.

E. NIH Office of Ethics' Review

1) Dr. Sunderland's unapproved outside activities with Pfizer was reviewed by the NIH Ethics Review Panel. The NIH Ethics Review Panel is composed of individuals with the expertise to evaluate matters related to ethical conflicts. The Panel documented in its memorandum dated April 1, 2005, that it found a direct overlap between the subject matter of Dr. Sunderland's official area of research and scientific subject matter of his Pfizer consultancies. The members of the panel concluded that Dr. Sunderland would not have been given approval for these consulting activities. The panel expressed concern over Dr. Sunderland's dual relationship with Pfizer and that he entered into a Material Transfer Agreement (MTA) with Pfizer in 1998 while he maintained an ongoing consulting relationship. The panel noted that his lecturing activities, both those related to Pfizer and those with other companies, would most likely have been approved as the lectures did not overlap with areas of research that Dr. Sunderland oversees at NIH.

2) In a memorandum dated October 12, 2005, the NIH Ethics Review Panel advised that Dr. Sunderland's official duties constituted an overlap with services he provided to Astra Zeneca, Cerebus, CNS Inc., Johnson and Johnson, Lilly, Merz, Novartis and Warner Lambert and the Panel concluded that his activities with these companies would not have been given approval, if he had sought it.

Analysis:

Dr. Sunderland, through his attorney and his interview with OMA, maintains that there was no effort at deception and that other scientists, doctors and administrators did not give the Forms 450 and 520 attention. Dr. Sunderland maintains that there was no conflict of interest in relation to the research he oversees at NIH and his activities with Pfizer. He maintains that administrators knew of his consulting and lecturing activities. Dr. Sunderland stated that he was open about his relationship at Pfizer and took care to avoid the appearance of a conflict. Dr. Sunderland maintains that some relevant documents were lost in the administrative approval process and he cites that his secretary for some time period was less than capable. Dr. Sunderland provided a letter with notes, which he states indicates he did submit outside activities for approval. He stated that he signed the HHS Forms 520, *Request for Approval of Outside Activity* and submitted them to his secretary to fill-in the relevant information concerning his outside activities with Pfizer and other companies. He said he did not think he had to resubmit approvals for ongoing activities for Pfizer. He further stated in his interview with OMA that he gave letters to his secretary, and he assumed the activities were approved unless he heard otherwise. He said that he knew he should not engage in activities before hearing that they were approved, but he was very busy with his science as well as other administrative work. He also maintains and provided evidence that leave slips were vetted through administrative channels, but often did not appear on the official time and attendance record.

Dr. Sunderland placed the NIH in a position where it had to respond to allegations of impropriety, which compromised faith in the Agency and trust in our research. Dr. Sunderland violated ethics rules with regard to his relationship with Pfizer and engaged in relationships with Pfizer and many other organizations that would not have been approved had he submitted them for approval in accordance with the process for seeking approval of outside activities. Dr. Sunderland violated NIH and Commissioned Corps procedures and policies on multiple occasions (Pfizer reported 140 activities for which there were no approvals) all of which cannot be dismissed as administrative oversights or anomalies. Given that he acknowledges that he had concerns about administrative support, he should have ensured that forms were submitted to the NIMH ethics office and that approvals were given. Dr. Sunderland was aware of the NIH ethics process through ethics training and was ultimately responsible for ensuring that all activities were approved and all financial disclosures were made. Not disclosing over $ 500,000 in income was not an oversight or lapse in judgment but appears to be a deliberate decision not to comply with the rules, policies and procedures that are necessary to protect the NIH, its scientists and most importantly, its science.

Although Dr. Sunderland has acknowledged that he now understands the importance of the NIH ethics outside activity approval process, he has recently failed to submit his *Executive Branch Personnel Public Financial Disclosure Form (SF-278)* for the year 2004, which causes us to question whether he will ever comply with the NIH ethics rules

and regulations. It also causes us to question whether or not he has been forthright regarding his activities with OMA investigators. Dr. Sunderland's continued misconduct has compromised public support of numerous other NIH scientists who, despite administrative challenges, have managed to follow proper procedure and receive proper approvals.

Dr. Sunderland maintains that there was no conflict of interest with respect to his relationship with Pfizer, the MTA and NIH. He maintains that he made great efforts to avoid the appearance of such including removing himself from some decision making processes. Dr. Sunderland may have felt that he was taking appropriate precautions to ensure that he was not in conflict; however, that was not an assessment for him to make. As an NIH scientist and especially in his role as Chief of one of its branches, he is obligated to engage in the process the agency has set forth for making such determinations. In a memorandum dated April 1, 2005, Holli Beckerman Jaffe, J.D., Director of the NIH Ethics Office outlines the NIH Ethics Panel's concerns with regard to Dr. Sunderland's relationship with Pfizer and notes that no documentation exists to the fact that Dr. Sunderland took every precaution necessary to avoid the appearance of a conflict. The precaution that Dr. Sunderland should have taken was to notify the National Institute of Mental Health (NIMH) Ethics Office to ensure that proper approvals had been given. However, the NIMH Ethics officials were unaware of Dr. Sunderland's activities.

It has been determined by the Office of Human Resources that if Dr. Sunderland were a civilian employee his actions would lead to a recommendation for his proposed removal. Dr. Sunderland's long years of service and dedication to the agency and the science, his significant contributions over time, have all been considered as mitigations, but they are not sufficient to outweigh the seriousness of his misconduct and its effect upon the agency.

Tab 33

To: NIH Ethics Office
Attention: Jon Donnelly, J.D.

From: Karen T. Putnam
National Institute of Mental Health, Geriatric Psychiatry Branch (NIMH GPB)

December 7, 2004

Kindly note the following two corrections for your records. From the very first inquiry by the NIH Office of Management Assessment (OMA), I fully acknowledged that I served as a consultant to Pfizer from January 2001 to June 2004. As of June 2004, I have ceased all outside consultant activity with Pfizer. In addition, my degree during this period was a B.S. not a Ph.D. or an M.D. I have recently received a Master's (M.S.).

Pfizer asked me to consult in the fields of statistics and data management. I was involved in specific projects exploring proteomics and statistical methodology. The Pfizer activities centered around discovery research, where the results were used to generate future hypotheses and directions of research. The results generated from my Pfizer outside activities were not part of the data involved in my current government job. All proteomics data were confidential and kept at the Pfizer site. The computer software and hardware used in exploring proteomics data was located at the Pfizer site. The initial proteomics data analyzed had been assayed approximately 2 years prior to starting my consultant agreements. I worked with the Pfizer statisticians and researchers, and did not do primary data analyses. My responsibilities focused on evaluation of statistical results and the methods applied to distinguish between healthy controls and Alzheimer patients, or on the rates of progression in Alzheimer disease. The primary similarities of my Pfizer outside activities to duties in my government job were that they both involved Alzheimer's disease and statistical methodology.

My official government job responsibilities with the NIMH GPB during this time period involved the statistical analyses and data management for GPB data. The scope of these data includes demographic, neuropsychological, sMRI, biological, genetic and cerebrospinal fluid data. I do not evaluate any drugs for protocol consideration, nor does the GPB have any protocols with a Pfizer drug. I work to ensure the integrity of GPB data, apply appropriate statistical analyses to the data and then organize results in a meaningful fashion for the Primary Investigator; conferring with our outside statistician when necessary.

If there are any additional questions please feel free to contact me.

Sincerely
Karen Putnam

Tab 34

ARNOLD & PORTER LLP

202.942.5000
202.942.5999 Fax
555 Twelfth Street, NW
Washington, DC 20004-1206

May 10, 2006

CONFIDENTIAL

HAND DELIVERY

Alan M. Slobodin
Senior Oversight Counsel
Committee on Energy and Commerce
2125 Rayburn House Office Building
Washington, DC 20515

Re: Sunderland Matter/Answers to Factual Inquiries

Dear Mr. Slobodin:

On behalf of Pfizer, Inc. ("Pfizer") this letter responds to your recent factual inquiries regarding Pfizer's contractual arrangements with the National Institute of Mental Health and Dr. Trey Sunderland.

Below we restate your inquiries in italics, followed by our responses.

1. *Please comment on what obligation, if any, Pfizer had to return or reject the inadvertent disclosure by NIH of patient names.*

At the time that the NIH disclosure occurred, the Health Insurance Portability and Accountability Act ("HIPAA"), which established requirements regarding the use and disclosure of Protected Health Information, was not yet in effect, and thus there was no legal obligation imposed upon Pfizer to return or reject the information received. Even under the current HIPAA requirements, Pfizer's research and development organization is not a "covered entity," and the duties imposed on such persons inadvertently receiving protected information are not clear. However, we believe Pfizer handled the inadvertent disclosure appropriately by creating an code to de-identify patients in the course of the research effort.

2. *Please confirm that the April 1998 MTA, with the subsequent amendment in October 2000, was the only MTA Pfizer entered into in connection with the Sunderland/NIH collaboration.*

Our records confirm that in connection with the Sunderland/NIH collaboration, Pfizer entered into only one MTA, with one subsequent amendment.

3. *Provide Pfizer's view on why the October 2000 amendment to the MTA was not structured in an official NIH MTA format and was sent to Dr. Sunderland's home address, instead of to NIH.*

The format of the amendment was the standard Pfizer letter format used at that time for amending agreements. At the time the amendment was executed, Pfizer was not aware of any official format for amending MTAs. Pfizer has no records to indicate exactly why Dr. Sunderland's home address was used for the MTA amendment. However, once Pfizer understood that Dr. Sunderland had the authority to sign the agreement (see response to question 4, below), the address of the letter may not have been considered important, and was likely chosen at the request of Dr. Sunderland.

4. *In April 1998, what was Pfizer's understanding of Dr. Sunderland's authority to sign an MTA?*

In 1998, Pfizer sought to confirm Trey Sunderland's authority to enter into the MTA on behalf of NIH. In this regard, Pfizer's Kathy Smith was referred to Kathy Conn at NIH who, to Kathy Smith's recollection, confirmed that Dr. Sunderland was authorized to execute the agreement. It has been Pfizer's standard practice when dealing with academic institutions, including institutions such as NIH, not to accept an investigator's claim to have authority to sign an agreement without consulting with an appropriate representative of the contracting institution.

5. *For the following areas -- unknown biomarkers, known biomarkers, consulting relating to drug development and Aricept®, and speaking activities -- please provide the following information: (1) the total amount of consulting fees provided in that area over the entire time period Dr. Sunderland was engaged by Pfizer; and (2) a brief description of the work that was done in that area by Dr. Sunderland.*

Table 1 provides a listing of the fees paid to Dr. Sunderland based upon the records currently available to Pfizer, including descriptions of each area of consulting.

* * *

We respectfully request that this information be held as confidential to the maximum extent possible under all applicable laws and regulations, including but not limited to, the rules of the Committee on Energy and Commerce.

We hope this fully responds to your requests.

Sincerely,

Daniel A. Kracov

cc: David Nelson

CONFIDENTIAL

TABLE 1:
DESCRIPTION OF SERVICES PROVIDED
BY DR. TREY SUNDERLAND TO PFIZER INC
AND RELATED FEES PAID

May 10, 2006

Nature of Services	Time Period	Total Consulting Fees/ Honoraria Paid[1]	Description of Services Provided
One-day consultancy to assist in discovery research program in the area of clinical markers of Alzheimer's Disease	September 25, 1997	$2,500.00	Dr. Sunderland visited Pfizer in Groton, CT to discuss clinical markers of Alzheimer's Disease.
One-day seminar	October 7, 1999	$1,000.00	Dr. Sunderland conducted a seminar entitled "People at Risk for Alzheimer's Disease: Clinical Measures and Potential Biomarkers."
Consulting Services for Pfizer's Known Biomarkers Project	November, 1998 to November, 2003	$125,000.00	Dr. Sunderland lent his expertise to analyzing data related to Abeta42, Abeta40, Tau, pTau, NSE and total protein results from the known biomarker project. He generated analysis plans and strategies and provided expert interpretation of the data. He would provide feedback on how the Abeta (etc.) results from the known biomarker project might correlate with other types of data associated with the samples (e.g., genotype, imaging, cognitive, neurochemical, etc). Dr. Sunderland also provided advice on what biomarkers might have the most value in differentiating Alzheimer's Disease from controls.

[1] Pfizer reimbursed Dr. Sunderland for travel expenses in connection with some of the services enumerated on this chart. However, due the manner in which Pfizer maintains such records, it is difficult to link a given travel reimbursement with a particular service rendered. Therefore, the above figures are exclusive of any travel reimbursement Pfizer may have provided to Dr. Sunderland in connection with the services he provided to the Company.

Nature of Services	Time Period	Total Consulting Fees/ Honoraria Paid	Description of Services Provided
Consulting Services for New Clinical Markers of Alzheimer's Disease	May, 1998 to May, 2003	$160,000.00	Dr. Sunderland lent his expertise to analyzing data related to new clinical markers of Alzheimer's Disease. He generated analysis plans and strategies, and provided expert interpretation of the data. In particular, he generated the subgroupings of patients that might provide insight into what markers might be useful for disease progression/early identification. Dr. Sunderland also provided advice on what potential biomarkers might have the most value in differentiating Alzheimer's Disease patients from controls, and what types of populations we should study to identify markers for progression of the disease.
Speaking Programs	March, 1996 to August, 2004	$311,150.00	Dr. Sunderland was provided honoraria for speaking engagements on behalf of Pfizer to audiences consisting of healthcare professionals. The purpose of the speaking engagements was to educate healthcare professionals about Alzheimer's, his research, and indicated uses for Pfizer's products.
Participation on Various Pfizer-Sponsored Advisory Boards	March, 2000 to March, 2004	Approximately $1,500.00-$2,500.00 per day	Dr. Sunderland received payments for his advice on Pfizer's development of its medical, marketing and/or sales strategy for a Pfizer product. Please note that Pfizer does not maintain records of individual payments to doctors who participate in Advisory Boards. Pfizer contracted with medical communications companies to handle the logistics (date, venue, payments, etc).
Academic Advisory Boards	1999, 2000, 2001	Approximately $2,000.00 per year	Dr. Sunderland agreed to participate on Pfizer Academic Advisory Boards. In this capacity, Dr. Sunderland reviewed grants and assisted Pfizer in determining which grants merited the Pfizer's support. Please note that Pfizer does not maintain records of individual payments to doctors who participate in the Advisory Boards. Pfizer subcontracted with medical communications companies to handle the logistics of these meetings.

Tab 35

Feb-15-2006 06:50pm From-Assistant Secretary for Legislation 202-690-7380 T-118 P.003 F-213

DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

National Institutes of Health
Bethesda, Maryland 20892
www.nih.gov

April 1, 2005

TO: Colleen Barros
Deputy Director for Management, NIH

FROM: Holli Beckerman Jaffe, J.D.
Director, NIH Ethics Office

SUBJECT: Dr. Trey Sunderland's Unapproved Outside Activities with the Pfizer, Inc.

Between May 1998 and June 2004, Trey Sunderland, M.D., Chief, Geriatric Psychiatry Branch, National Institute of Mental Health (NIMH), engaged in a series of unapproved speaking and consulting activities with Pfizer, Inc. After a careful review of Dr. Sunderland's unapproved outside activities with Pfizer, the Panel finds a direct overlap between the subject matter of Dr. Sunderland's official area of research and the scientific subject matter of his Pfizer consultancies. The members of the Panel conclude that he would not have been given prior approval for the consulting activities. In addition, the panel expresses further concern over the Material Transfer Agreement (MTA) that Dr. Sunderland entered into with Pfizer in 1998 while he maintained an ongoing consulting relationship with the company in the same area. With regard to the one-time speaking events, however, the Panel concludes that the single lectures given by Dr. Sunderland would have been approved, because the topics of those lectures were general and lacked specific overlap with Dr. Sunderland's work at the NIH.

Unapproved Consulting

As the Chief of the Geriatric Psychiatry Branch at NIMH, Dr. Sunderland has been conducting research on Alzheimer's disease and studying depression in the elderly since 1982. As part of that research, he studies the development of potential biomarkers for Alzheimer's disease. From 1998 to 2004, Dr. Sunderland consulted for Pfizer on the development of central nervous system products, and according to his consulting agreements with the company he focused in particular on biomarkers for Alzheimer's disease. In a letter from Dr. Sunderland's attorney to the NIH Ethics Office, his attorney states that "Dr. Sunderland has been working with Pfizer as a consultant to consider alternative approaches [to traditional Alzheimer's disease medication trials] that would include different and multiple dependent variables, including surrogate markers, in medication and efficacy trials." The NIH Ethics Review Panel finds this type of consulting work to be directly related to Dr. Sunderland's research at the NIH and concludes that he would not have received approval to serve as a consultant with Pfizer in this area.

Dr. Sunderland however draws a distinction between the study of "surrogate markers", which he says are the subject of his consulting with Pfizer, and his study of "*biomarkers*" at the NIH. In a letter to the NIH Ethics Office, Dr. Sunderland's attorney states that "although these two terms (biomarkers and surrogate markers) may share semantic overlap and are often mistakenly interchanged in casual scientific discussion, the goals and techniques employed with biomarkers

research and surrogate marker trials are quite different." The Panel disagrees and does not find a significant distinction between "surrogate markers" and "biomarkers" for the purposes of the determination of overlap between the subject matter of the activities and Dr. Sunderland's official duties.

The Panel explains that a "surrogate marker" is a specific type of biomarker, and at the NIH, Dr. Sunderland studies a range of biomarkers related to Alzheimer's disease. Even if he did not study the same biomarkers as in his Pfizer consultancy – which it is not clear that he did not – the distinction that he draws between the study of different biomarkers is too fine to provide a meaningful basis to differentiate the subject matter of the unapproved consulting activities and his official duties. The study of surrogate markers for Alzheimer's disease constitutes the same area of research as his work at the NIH.

Furthermore, the Panel is deeply concerned by Dr. Sunderland's dual relationship with Pfizer. As noted above, Dr. Sunderland served as a consultant to Pfizer from 1998 to 2004. In 1998, Pfizer and Dr. Sunderland, on behalf of the NIMH (he signed the agreement as the authorized signatory for the NIMH), entered into a MTA. In his official capacity as Chief of the Geriatric Psychiatry Branch, Dr. Sunderland officially transferred coded clinical samples of cerebrospinal fluid to Pfizer. The samples were from subjects that took part in previous NIH clinical trials involving Alzheimer's disease. After obtaining the samples, Pfizer scientists studied them for Alzheimer's biomarkers and published the results in an April 2003 edition of the *Journal of the American Medical Association*. Dr. Sunderland, in his official capacity, appeared as co-author to the article along with the Pfizer scientists.

Dr. Sunderland contends that the MTA did not occur as a result of his prior relationship with Pfizer. In a letter from his attorney, Dr. Sunderland asserts that Dr. Friedman, a Pfizer scientist, initiated contact with Dr. Sunderland based upon his knowledge of Dr. Sunderland's published work in the field of Alzheimer's research and that the scientist works in a different division of Pfizer, unrelated to Dr. Sunderland's consulting work with the organization. In vetting the MTA for approval, Dr. Sunderland states that he took every precaution to avoid the appearance of a conflict. Despite his assertions, no documentation exists to that effect, and NIMH ethics officials have indicated that they were unaware of his activities with Pfizer. Whether the MTA was facilitated because of Dr. Sunderland's outside relationship with Pfizer is irrelevant. The ethics rules do not allow an employee to participate in an official duty matter involving the same company to which he serves as a consultant without authorization to do so. There is no record of such authorization.

Unapproved Lectures

In addition to Dr. Sunderland's consulting activities, he participated in (and received compensation for) numerous lectures for Pfizer from 1998 to 2004. The lectures were on the topics of Alzheimer's disease and depression in the elderly and could best be compared to continuing medical education lectures commonly attended by medical practitioners. Dr. Sunderland provided evidence that these lectures were of a general nature and did not involve the marketing of Pfizer products.

The Standards of Conduct prohibit an employee from receiving "compensation from any source other than the Government for teaching, speaking or writing that relates to the employee's

official duties." 5 C.F.R. §2635.807(a). A speech "relates to an employee's official duties if: . . . the subject of the activity deals in significant part with: (1) any matter to which the employee presently is assigned or to which the employee had been assigned during the previous one-year period." 5 C.F.R. §2635.807(a)(2)(i)(E).

According to this standard, the Ethics Review Panel concludes that the subjects of the lectures do not overlap with the areas of research that Dr. Sunderland oversees at the NIH. The Panel finds that the lectures are very general in nature and contain information for a wide audience. Although the numerous unapproved lectures for Pfizer represent a huge pattern of disregard for the prior approval rules by Dr. Sunderland, because the subject matter only involves information related to Dr. Sunderland's NIH research in a very general way, the members of the Review Panel conclude that the lecturing activities would likely have been approved if he had sought such approval.

The NIH Ethics Review Panel does note, however, that in a sample set of presentation slides provided by Dr. Sunderland, he appears to be referring audience members to clinical trials at the NIH. Recruiting for clinical trials as part of an outside activity is prohibited. In discussing an NIMH protocol relevant to one of his lectures, Dr. Sunderland provides the name and telephone number of a coordinator at the protocol. Presenting this type of information during a paid outside lecture may be contrary to NIH policy if the mentioning of the protocol is determined to be recruiting of patients.

Holli Beckerman Jaffe, J.D.

Tab 36

Feb-15-2006 08:50pm From-Assistant Secretary for Legislation 202-690-7380 T-118 P.002 F-213

02/14/2006 11:27 FAX 301 480 2281 001

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

National Institutes of Health
Bethesda, Maryland 20892
www.nih.gov

May 10, 2005

TO: Colleen Barros
Deputy Director for Management, NIH

FROM: Director, NIH Ethics Office

SUBJECT: Karen Putnam's Unapproved Outside Activity with Pfizer

The NIH Ethics Review Panel examined an unapproved outside consulting activity between Pfizer and Karen Putnam, Research Assistant, Geriatric Psychiatry Branch, National Institute of Mental Health (NIMH). The Panel finds a significant overlap between the scientific subject matter of the consulting activity with Pfizer and Ms. Putnam's official duties.

Between January 2001 and June 2004, Karen Putnam served as a consultant for Pfizer and was involved in projects related to the study of its Alzheimer's drug Aricept. Ms. Putnam entered into a consulting agreement with Pfizer to advise the company on statistics and data management for studies investigating "biomarkers for neurological disease." She worked specifically with Pfizer statisticians and researchers to evaluate the statistical results and the methods applied to distinguish between healthy controls and Alzheimer's patients and to evaluate the company's data on the rates of progression in Alzheimer's disease.

At NIMH, Ms. Putnam's official duties include statistical analysis and data management for the Geriatric Psychiatry Branch (GPB), which focuses on the study of biomarkers for Alzheimer's disease. She works to ensure the integrity of GPB data, applying appropriate statistical analyses to data that captures a range of information from GPB studies on Alzheimer's disease.

Even though Ms. Putnam does not work in drug testing nor with any Pfizer drugs, the Ethics Review Panel finds that the scientific subject matter of her unapproved outside activity with Pfizer is too close to her official responsibilities at NIMH. The Panel finds that she works in the same scientific area, which deals directly with the study of biomarkers for Alzheimer's disease, and that the research problems that she faces in her position at NIMH are very similar to the work that she did for Pfizer, which was to advise the company on its statistical methodology for the study of biomarkers for Alzheimer's disease. Accordingly, the Panel concludes that Ms. Putnam would not have received approval for the activity, if she had sought it, because her official duties overlap with the scientific subject matter of the consultancy with Pfizer.

Holli Beckerman Jaffe, J.D.

cc: Suzanne Servis, OMA

Tab 37

Slobodin, Alan

From: Flamberg, Gemma (NIH/OD) [E] [FlamberG@OD.NIH.GOV]
Sent: Thursday, June 01, 2006 4:09 PM
To: Slobodin, Alan
Cc: Hemard, Casey (OS); Smolonsky, Marc (NIH/OD) [E]
Subject: tissue sample investigation -- follow-up question

QUESTION: The MTA with Pfizer was co-signed by Dr. Robert Desimone on February 24, 1999. Did Dr. Sunderland get a copy of the MTA with Dr. Desimone's signature?

RESPONSE: NIMH technology transfer staff, past and present, have no evidence that they ever gave Dr. Sunderland a copy of the 1998 MTA after Dr. Desimone had signed it. NIMH also asked Dr. Sunderland whether he had ever received a copy, and he said that he had not received a copy until several months ago when he requested that Bill Fitzsimmons provide it to him.

Gemma Flamberg
Senior Legislative Analyst
Office of Legislative Policy and Analysis
National Institutes of Health
(301) 496-3471
fax (301) 496-0840
flamberg@od.nih.gov

Tab 38

NIH TECHNOLOGY TRANSFER AND YOU

The primary mission of the NIH is to acquire new knowledge through the conduct and support of biomedical research to improve the health of the American people. In pursuing this mission, NIH scientists often discover new technologies. The process of sharing these new technologies with other organizations and the public is called technology transfer. Although not all inclusive, the sharing of new research materials with colleagues, the pursuit of collaborative relationships with outside entities, and the awarding of intellectual property rights to commercial entities for development and commercialization, are all considered technology transfer activities.

Federal technology transfer is governed by a comprehensive set of laws, regulations, and policies. To ensure awareness and compliance with those requirements, every Institute/Center (IC) has designated a Technology Development Coordinator (TDC) who assists IC scientists with technology transfer issues. Your TDC is available to discuss any discovery, proposed collaborative working relationship or sharing of materials.

The following are highlights of some key activities and issues involved in technology transfer.

Material Transfer Agreements (MTAs) NIH uses this mechanism when there is an exchange of materials without an exchange of intellectual property rights. An MTA protects the scientist and the NIH against improper use of materials. It also helps to protect the confidentiality of the material. ***Current NIH policy requires that MTAs be used whenever an NIH scientist sends out or receives materials, e.g. cDNAs, cell lines, antibodies, etc. These agreements must be signed by authorized IC personnel.***

The Uniform Biological Material Transfer Agreement (UBMTA) is an MTA that NIH and more than 120 institutions have agreed to use. For institutions which have signed the UBMTA Master Agreement, materials can be transferred upon execution of an Implementing Letter. For further information, contact your IC TDC.

Cooperative Research and Development Agreements (CRADAs) CRADAs are a mechanism used by NIH scientists to collaborate with other organizations **outside of NIH**. CRADAs allow the exchange of resources including materials, personnel, and equipment among the parties and may confer intellectual property rights. Additionally, funds can be transferred to, but not from, the NIH laboratory/branch to assist in carrying out the project. Since CRADAs involve important legal and ethical constraints on the scientist and the research project, there is a formal clearance process for all NIH CRADAs. A scientist contemplating the use of a CRADA should contact their IC TDC.

Inventions Inventions arise from new discoveries including, but not limited to, vaccines, diagnostics, devices, compounds, research tools, compositions of matter, or any new and useful improvements on existing technologies. ***Inventions made by Federal employees and persons under certain other types of appointments belong to the Federal Government and, as required by 45 CFR 7.1, must be reported by using the PHS Employee Invention Report (EIR) Form PHS 6364.***

Patents NIH may seek a patent on a reported invention when it is necessary to facilitate and attract investment by commercial partners for further research and commercial development of the technology.

Dates are critical in patent law because disclosures such as posters, abstracts, talks, public databases or published manuscripts made prior to filing a patent application with the appropriate patent offices may eliminate NIH's ability to obtain comprehensive patent **protection** on an invention. ***If you believe you have a new invention, it is important to contact your IC TDC who may suggest that you file an Employee Invention Report (EIR) as soon as possible. If an invention exists, there is no reason to wait until preparation of a scientific paper or scheduling of an oral/poster presentation before an EIR is filed.***

Licences A license is a mechanism used by NIH to award NIH intellectual property rights to a commercial entity. NIH may seek to license a new technology reported by an employee whether or not that technology is patented. NIH seeks to ensure the development of technologies and the availability of research tools to advance further scientific discovery through the use of various types of licenses.

Royalty Distribution NIH provides financial incentives to inventors from royalty income received under licenses to their inventions. NIH inventors share the first $2,000 of royalty income received under a license and a percentage thereafter up to a maximum of $150,000 in royalty income per inventor per year. The remaining income is returned to the IC for use as prescribed by law.

Confidentiality This is an important issue in technology transfer since these adivities involve considerable interaction with the private sector. Collaborative agreements, patents, and licenses all require some degree of confidentiality which must be carefully considered and balanced to ensure a thriving scientific enterprise. Confidential Disclosure Agreements (CDAs), signed by ICs and other organizations, are one mechanism which allows signatories to freely exchange information which could be beneficial to the scientific and public health mission of the NIH yet insure that information is not made available to the public prior to official disclosure.

Ethics As stewards of the public trust, Federal employees must always be aware of practicing ethical behavior. This is particularly important for NIH scientists participating in technology transfer activities. NIH scientists must be vigilant in ensuring that they are not using public resources for private and personal gain. NIH scientists should consult their IC TDC and/or Ethics Officer when contemplating technology transfer activities.

To learn more about your rights and responsibilities regarding technology transfer, consult your Institute's Technology Transfer Office:

NIMH Technology Transfer Office Staff:
TTO Director: Kathleen M. Conn
Technology Transfer Specialist: Suzanne L. Winfield, Ph.D.
Technology Development Administrative Specialist: Joyce L. Williams

Phone: 496-8828 FAX: 480-1384
Mailing Address: Building 10, Room 4N222

NIMH Technology Transfer Office Web Site:
http://intramural.nimh.nih.gov/techtran

You may also wish to review the information on the NIH Office of Technology Transfer Web Site: www.nih.gov/od/ott/

NIMH Version Revised 2/24/00
Approved by TTPB on 11/19/98

Tab 39

	A	B	C	D	E
1					Visit to Pfizer Date
2	KAREN PUTNAM	2/8/2001	$15,000.00	Consulting fee	
3	KAREN PUTNAM	2/21/2001	$1,000.00 *	Consulting fee	January 2nd, 2001
4	KAREN PUTNAM	2/26/2001	$976.00 *	Consulting/expenses	
5	KAREN PUTNAM	3/19/2001	$1,000.00 *	Consulting fee	February 16th 2001
6	KAREN PUTNAM	3/28/2001	$903.85 *	Consulting/expenses	
7	KAREN PUTNAM	8/17/2001	$2,000.00 *	Consulting fee	July 23rd, 2001
8	KAREN PUTNAM	8/17/2001	$1,163.30 *	Consultant expenses	
9	KAREN PUTNAM	1/22/2002	$1,247.18 *	Consultant expenses	November 19th-20th, 2001
10	KAREN PUTNAM	1/23/2002	$2,000.00 *	Consulting fee	
11	KAREN PUTNAM	8/13/2002	$1,523.06 *	Consulting/expenses	June 23-24th, 2002
12	KAREN PUTNAM	9/10/2002	$15,000.00	Consulting fee	
13	KAREN PUTNAM	2/27/2003	$2,159.56 *	Consulting/expenses	January 20th 2003
14	KAREN PUTNAM	7/17/2003	$6,000.00 *	Consulting fee	
15	KAREN PUTNAM	2/25/2004	$15,000.00	Consulting fee	
16					
17					

	F
1	Comments
2	2001 - For teleconferences, sample shipments and data anlaysis
3	Visit to Pfizer
4	
5	Offsite at Mystic Hilton
6	
7	Visit to Pfizer
8	
9	Visit to Pfizer
10	
11	Visit to PFizer
12	2002 - For teleconferences, sample shipments and data anlysis
13	Visit to Pfizer
14	For 6 months of 2003. The $6000 is half-year consultancy. For teleconferences, sample shipments and data anlys
15	2004 - For teleconferences, sample shipments and data anlysis
16	
17	

Tab 40

Smith, Kathryn E

From: Friedman, David L
Sent: Friday, August 07, 1998 1:51 PM
To: Smith, Kathryn E; Silber, B Michael; Williams, Stephen A; Stiger, Thomas R
Cc: Pun, Edward F; Durham, L Kathryn
Subject: RE: Number of variables in NIH database

Tom,

I contacted Trey on Monday, and am awaiting a response. Give me another day or two and I will get this information.

David Friedman

Mike,

I suggest that David or/and I (as Steve is away until the 17th) contact Trey before Katey and I go to OGS (we are departing the evening of the 11th) to see if he has given further thought to what other variables he would or can include. This was more or less an action item for him based on conversations after the steering committee meeting (from what recall). David - how about us following up with him on this, via a call or e-mail. I won't be able to squeeze a visit in to NIH between now and the OGS visit.

Tom

ENTERED

-----Original Message-----
From: Silber, B Michael
Sent: Friday, August 07, 1998 12:20 PM
To: Stiger, Thomas R; Williams, Stephen A; Friedman, David L; Kathryn E Smith at CR_GROTON_NONCLIN12
Subject: RE: Number of variables in NIH database

Tom,

This is the same situation we can't seem to get out of because of Trey's unwillingness to be forthcoming. I suggest you seriously consider visiting him at NIH and discussing with him how we need to get the information now in order to not create an undue hardship on OGS. I believe the time has come to bite the bullet on this otherwise it will just continue. I don't see how we can avoid this situation any longer without us looking silly with OGS. Whatever you do, please do not copy OGS in these communications relating to Sunderland.

Any other thoughts?

Michael

_____ Reply Separator _____
Subject: Number of variables in NIH database
Author: Thomas R Stiger at Groton-CR
Date: 8/7/98 10:44 AM

Dave and Steve,

Katey and I had our usual teleconference with Athula at OGS today. Chris Ashton

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and Reid Townsend also participated and brought up the issue of the number of variables that will be included in the NIH database. Specifically, for the aid of planning, they wanted to know if there were to be more variables than what we currently have (I sent them a listing of the variables we currently have). They indicated that it would be very helpful, if they knew the maximum number of variables that this database will have, and the nature of the variables (e.g., chemistries). Backpopulating their database will be problematic for them if they receive more variables than they have planned for. I indicated that we would probably have some more variables such a autopsy confirmed AH, and possible some other cognitive scales. Based on what I recall, Trey was going to look at his data and reassess what other variables he/us might want to include. Has there been any updates on this? As soon as we finalize the what variables are to be included, we need to communicate this to OGS.

Thanks, Tom

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Tab 41

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December 8, 2004

CONFIDENTIAL

Holli Beckerman Jaffe, JD, Director
NIH Ethics Office
Bldg 2, Room BE-21
31 Center Drive, MSC 0201
Bethesda, MD 20892-0201

Via Fax and E-Mail

Re: Dr. Trey Sunderland

Dear Ms. Jaffe:

We have had several discussions regarding the Ethics Office's request for information from Dr. Trey Sunderland. In this letter, we respond to the particularized requests set forth in an e-mail dated November 23, 2004, from Jon Donnelly of your office, as well as the matters we discussed on the telephone. It is our understanding that these requests are in furtherance of the ongoing investigation being conducted by the Office of Management Assessment (OMA) which likewise has been reviewing Dr. Sunderland's, as well as scores of other doctors', outside activities.

Introduction

Since June, Dr. Sunderland (like many other NIH doctors and scientists) has responded to OMA inquiries and been interviewed by that office. To that end, I

enclose letters previously submitted to OMA.[1] We assume that you have access to Dr. Sunderland's interview, conducted by Ms. Quast and Mr. Hainer at the NIH offices on August 19, 2004. If you do not, let me know and I will promptly get you OMA's summary. From that and our several submissions, the following conclusions can be drawn from the investigation to date:

- Numerous doctors and administrators (including OMA's investigators) have described outside activities reporting at NIH as a "system that was broken."
- There was a lack of attention among the NIH professional staff to various reporting forms. Dr. Sunderland, other scientists/doctors, and the administration in general did not always give this subject the attention it is now receiving.
- Dr. Sunderland was open and obvious regarding his relationships with Pfizer and other pharmaceutical companies. He was not hiding these relationships, and many people at the NIH, including administrators, were fully aware of the fact that Dr. Sunderland both lectured and consulted for Pfizer.
- As set forth herein, Dr. Sunderland had no conflict of interest in the discharge of his duties and functions at the NIH. To the contrary, he was affirmatively careful to note them and to make certain his scientific research was not compromised by any conflicts.

The OMA investigation, in the main, has related to the manner by which Dr. Sunderland met his obligations for filing disclosure forms, e.g., 450's and 520's. Your inquiry puts a sharper focus on the issue of "overlap" or (as we discussed in our telephone conversations) the more pointed question of whether Dr. Sunderland had any conflict of interest as he dealt with Pfizer. In our telephone conversation, you elaborated on the matter of overlap, suggesting we review Dr. Sunderland's circumstances by describing what he did at NIH and what he did on behalf of Pfizer. To ensure a thorough response, we provide the following:

[1] See letter dated July 9, 2004, to William Fitzsimmons from Robert F. Muse; letter dated August 31, 2004, to Patricia Quast and Arthur Hainer from Robert F. Muse; letter dated October 4, 2004, to Suzanne Servis from Robert F. Muse; and letter dated October 28, 2004, to Patricia Quast from Robert F. Muse.

1. A summary of Dr. Sunderland's Official Duties at NIH.
2. A description of Dr. Sunderland's Outside Activities with Pfizer.
3. A description of the Material Transfer Agreement ("MTA") between Pfizer and NIH.
4. A discussion of why there was no conflict of interest.

A review of Dr. Sunderland's activities will demonstrate that he had no conflict of interest as he discharged his functions as an NIH doctor. While there was an overlap to the extent that his very role at NIH, as a leading scientist in the area of Alzheimer's research and geriatric psychiatry, allowed him to both speak for, and consult with, Pfizer on matters related to Alzheimer's Disease, there was no legal or ethical conflict. In the one instance where Pfizer could possibility have gained an advantage in its dealings with NIH, viz., the scientific collaborations authorized by the MTA, Dr. Sunderland properly and promptly removed himself from the decision making process. Dr. Sunderland was careful to note that he had an ongoing relationship with Pfizer and thus deferred to others at NIH the decision to award any MTA benefits to Pfizer. As to his speaking and consulting roles for Pfizer, nothing in either setting conflicted with his NIH duties.

1. **Dr. Sunderland's Duties at NIH**

Dr. Sunderland serves as Chief of the Geriatric Psychiatry Branch of the NIMH. In that capacity, he coordinates and supervises a group of approximately 15 people who are focused on clinical research studies with the elderly. Specifically, they recruit and describe clinical populations of Alzheimer's disease (AD) patients and normal controls for various research protocols where Dr. Sunderland is the principle investigator. As you can see from his CV (attached), these studies cover a wide range of areas including the following topics:

- Pharmacologic challenge studies designed to test the sensitivity of AD patients and older controls (i.e., scopolamine, nicotine, m-CPP and examine).
- "Proof of concept" medication trials in select AD populations (i.e., l-deprenyl, naloxone and cyclophosphamide).
- Study of the biological, cognitive and psychological effects of spousal bereavement in elderly subjects.

- Characterization of biological and neuropsychological changes over time in AD and "at risk" control populations.

- Employment of structural and functional brain imaging (with R. M. Cohen, M.D., Ph.D.) as a possible marker of incipient and ongoing neurodegeneration in AD patients and controls.

Dr. Sunderland's Alzheimer's research provided no realistic basis for any conflict of interest involving Pfizer. At no time was any Pfizer drug studied in any of the protocols or research endeavors in Dr. Sunderland's branch. At no time did Dr. Sunderland have any authority or influence in the awarding of benefits to Pfizer or any other pharmaceutical company. At no time did Dr. Sunderland sponsor any Pfizer drug products as part of his clinical studies. Finally, the Geriatric Psychiatry Branch of NIMH had no grant authority; did not make specific recommendations regarding grants; and was not involved in any specific grant.

2. **Dr. Sunderland's Outside Activities with Pfizer**

As an initial matter, it is important to stress that, since approximately 1996, NIH doctors and scientists have been permitted to engage in, and receive payments for, education and consulting activities on behalf of private outside groups, including pharmaceutical companies. In this regard, NIH doctors have opportunities not typically available to other federal employees. Why is this? Much has been written and discussed about the issue of outside activities, but as an overriding matter there has been a recognition of several factors unique to the NIH community:

- It is important and beneficial to the NIH program that doctors and scientists be involved with the private scientific community to stay current with scientific advances.

- NIH doctors, in turn, have been able to spread information and make the private community and non-NIH academics aware of its research.

- In no small measure, outside activity opportunities have allowed NIH to competitively recruit and retain doctors who, in the private sector, would be able to earn significantly greater salaries than they would under the restrictive federal grade-pay scale.

Generally, these outside activities have taken the form of lecturing and

consulting. Dr. Sunderland availed himself of both opportunities but in no instance were these activities in derogation of his NIH duties. In the section that follows, we examine what Dr. Sunderland did as a speaker, e.g., when, why and to what end. We then examine his consulting activities.

Lecturing

Over the past decade, there has been a tremendous upsurge in the public's interest in the area of Alzheimer's disease. Dr. Sunderland is one of the world's leading clinical authorities on the subject. He is a highly sought after lecturer because of his broad knowledge of the area and because of his accomplished skills as a teacher and speaker. Pfizer's interest in having Dr. Sunderland as a lecturer is no different than its arrangement with scores of other doctors, including many from NIH. As part of its lecture programs, Pfizer is interested in bringing doctors together in various community settings. The best way to do this is to present a topical subject by a skilled lecturer. Dr. Sunderland fits that profile. Over the past five years (1999 – 2004), Dr. Sunderland, on average, gave between 25 and 30 lectures per year under the Pfizer Speakers Program. For this, he generally was paid $1,500 per lecture. In terms of these speeches, the following factors are important:

- At no time did Dr. Sunderland ever advertise, promote or encourage the use of a Pfizer product in an unbalanced way.

- Dr. Sunderland's speeches were notable for their lack of bias. There is not a hint that, in his many speeches and lectures, Dr. Sunderland favored Pfizer or any other drug company. Much to the contrary, audience evaluations following his speeches have consistently identified Dr. Sunderland as the least biased speaker. For example, at the 2004 APA national meeting in New York, Dr. Sunderland's presentation received the highest score in the category "provided an unbiased view." Indeed, it is his lack of bias generally that allows Dr. Sunderland to be one of the most respected national authorities on Alzheimer's disease.

- Frequently these speeches were grouped together, in a setting where Dr. Sunderland might give three or four speeches in a single 24-hour period. For example, on September 12, 2002, he was in Lynchburg, Virginia to give three lectures in one day; on April 11, 2003, he traveled to Ashville, N.C. and gave three lectures; on December 19, 2003, he was in New York City to give three presentations. By approaching his lecturing work on this concentrated basis,

there was minimal interference with his work at NIH.

- The lecture work permitted Dr. Sunderland to advance NIH's interests in identifying its research to the public. Traveling and meeting physicians outside of NIH has also lead to the referral of scores of patients to participate in various studies. While there was no solicitation of research subjects during the lectures, the increased awareness of local physicians ultimately led to the secondary benefit of having patients aware of the NIH activity.

In tone and content, Dr. Sunderland's Pfizer lectures were similar to public speeches he gave for NIH, as well as to community groups and educational institutions for which he received no compensation.[2] In no respect did Pfizer receive a benefit on the basis of these speeches that would have been different from that conferred on the sponsoring group in an uncompensated setting.

Consulting

Dr. Sunderland also had a consulting role with Pfizer. This activity dates to the mid-1990s when the ban on consulting was lifted for NIH scientists. As with the educational lectures, Dr. Sunderland's expertise in geriatric psychiatry, in general, and Alzheimer's disease, in particular, is what makes him attractive as an adviser to the pharmaceutical industry. He is not a laboratory scientist, so his consulting necessarily must focus on the general strategy and specifics regarding clinical pharmaceutical development and not on issues related to laboratory science. Furthermore, he has taken care to avoid consulting for companies with products related to his ongoing research at the NIH to avoid any conflict of interest.

The consulting with Pfizer is generally described in several formal agreements previously furnished to OMA. These agreements cover a period of approximately five years, 1997 through 2002 and outline the subject matter of the consulting arrangements.[3] Dr. Sunderland was asked to consult in the area of Alzheimer's disease, as well as in the use of biomarkers in drug development. In at least one

[2] Prior to the change in the regulations in mid-1990s, Dr. Sunderland regularly gave lectures on behalf of Pfizer and other companies. It is noteworthy the nature of these lectures has not changed over the years. What did change was the way in which honoraria was treated. Prior to the change in the regulations, the fees went to a general fund at NIH.

[3] There are earlier agreements dating back further that could not be found in either Dr. Sunderland's or NIH's files. However, related documents that were located, contain handwritten notations by Dr. Sunderland which, as he has explained to OMA, indicate that he submitted the Pfizer consulting agreements for approval.

instance, the consulting agreement pertained to the even more general "development of CNS products and programs."

By executing the consulting arrangements, Pfizer established an on-going relationship with Dr. Sunderland for advice and counsel in various areas, including:

- Dr. Sunderland regularly advised Pfizer on the multiple current and future uses of donepezil (Aricept) in elderly populations. This consultation drew upon Dr. Sunderland's general expertise with the class of cholinesterase inhibitors in AD as well as particular knowledge and experience in the early clinical development of donepezil by a Japanese pharmaceutical company (Eisai) when it was still known as E2020. This background knowledge was not a part of Dr. Sunderland's official duties at the NIH, but was part of the reason that he was attractive as a consultant to Pfizer. Once more, it should be noted that neither Dr. Sunderland nor his research group ever participated in trials of donepezil or any other Pfizer medication as part of NIH official duties.

- Dr. Sunderland also provided strategic advice about new drug development for the elderly, including elderly depression, psychotic behaviors and Alzheimer's disease. Like any other pharmaceutical consultant from NIH, Dr. Sunderland brought his broad knowledge of the field, especially in AD research and depression. Presented with basic science data, animal study results and preliminary data from early human studies, Dr. Sunderland has advised Pfizer about the potential usefulness of its proprietary compounds.

- Dr. Sunderland consulted in a general manner on the development of drugs in AD research. Here, the focus is less on specific medications and more on the strategy involved in developing and testing new medications or classes of medications. This advice is important to Pfizer because one of the challenges for any pharmaceutical company in developing medications for a neurodegenerative illness like AD is the long time it takes to evaluate the clinical efficacy of any treatment. In fact, the length of clinical trials is a costly and rate-limiting factor in the entire development process. Generating new approaches to shorten the duration of clinical trials using various target markers is an obvious priority for companies like Pfizer, and Dr. Sunderland provided ongoing consultation about the development of such strategies. This consulting is quite different and separate from the exploration of peptide biomarkers for possible diagnostic and prognostic use in AD. Once more, it is noteworthy that Dr. Sunderland and the GPB research group do not focus on efficacy trials in

AD. Instead, they focus on "proof of concept" studies with non-commercial products.

Dr. Sunderland's consulting was both approvable and within the acceptable guidelines for such outside activity at NIH. It did not relate to his official or presently assigned duties at NIH. Instead, it was based on his accumulated expertise in Alzheimer's research and geriatric psychiatry. The information he utilized was neither proprietary nor confidential. His role with Pfizer was based on his well established scientific and medical reputation, not on his official position at NIH.

3. **Material Transfer Agreement between Pfizer and NIH**

In early 1998, Dr. Sunderland was approached by Dr. David L. Friedman of Pfizer, who was seeking access to cerebrospinal fluid samples (CSF) for a scientific collaboration. This was not an unusual request. Because the Geriatric Psychiatry Branch is a clinically-focused group, the laboratory component of the research is usually accomplished via collaboration. For example, Dr. Sunderland has established over 30 such collaborations (including several with private pharmaceutical companies) during the last 23 years to study various components of the cerebrospinal fluid gathered in his clinical studies of AD patients, elderly depressed subjects and normal controls.

From the Pfizer perspective, their investigators were interested in the proposed collaboration for the following reasons:

- Obtain access to samples from a well-described population of clinical subjects including Alzheimer patients and normal controls.
- The NIMH population is one of the larger collections of CSF from such subjects in the world.
- Proteomic exploration of CSF was designed to help discover new peptide targets for drug development with both scientific and potential commercial applications.

From the NIMH perspective, there were equally important but separate reasons for the collaboration:

- CSF beta-amyloid assays were not reliable or stable across various research centers (see Sunderland et al., JAMA 2003 for meta-analysis), and Pfizer scientists offered Dr. Sunderland a stable assay ready-made for cross-sectional and longitudinal studies.

- Commercial assays were expensive (approximately $500/sample), so the cost for the over 2000 samples involved in this study would have been impossible given the budget of the Geriatric Psychiatry Branch. The NIH cost savings with the MTA collaboration is estimated at $1,000,000 over the last 5 years.

- This collaboration offered an exciting opportunity to engage in exploratory proteomics with automated 2D-gel electrophoresis and cutting edge computerized image quantification of the resultant gels. This opportunity was available with the Pfizer collaboration through a third party, Oxford Glycosciences, which had proprietary technology not available anywhere else in the world. The pursuit of 2D-gel electrophoresis study of CSF peptides had been a scientific interest of Dr. Sunderland's since the early 1980's, as demonstrated by numerous previous CSF collaborations.

- The MTA represented the kind of NIH/pharmaceutical collaboration that was encouraged within the NIH community to promote cooperation across traditional government/industry boundaries and to pursue translational research.

At the time of his inquiry, Dr. Friedman was not aware that Dr. Sunderland had any prior association with Pfizer. Dr. Sunderland promptly notified Dr. Friedman of this, and stated that he would not be able to undertake any actions with regard to the collaboration until such activity was cleared and approved by NIH. In turn, Dr. Friedman's goal was to make sure that the business, medical and administrative people at NIH were fully informed. To this end, Dr. Sunderland's ongoing outside activities with Pfizer was discussed with representatives of NIH and by all parties. There was no effort to hide Dr. Sunderland's role. A process that consumed many weeks of discussions and an exchange of many documents clarified the best way to effectuate the Pfizer – NIH collaboration, with a critical point being that there be no conflict involving any NIH doctors, in terms of outside activity with Pfizer.

Dr. Sunderland was open about his circumstances, and did not disguise or minimize his relationship with Pfizer. To the contrary, he affirmatively directed that this matter be cleared by NIH, before any joint venture was established between NIH and Pfizer. This, in fact, was done. If asked, Dr. Friedman would report that Dr.

Sunderland was "forthright, open and transparent" in all his dealings on behalf of NIH; was "insistent" that there be full disclosure of the relationships Dr. Sunderland had with both Pfizer and NIH; and "was uncompromising" in his requirement that Dr. Friedman and NIH fully review all ethical issues, including conflicts with both Pfizer and NIH to make sure that the process was handled "correctly". Dr. Friedman saw Dr. Sunderland as an "exemplary doctor" who "well served his patients." On this last point, Dr. Friedman was struck by the fact that Dr. Sunderland was "unusually dedicated to his patients" as he discharged his NIH functions.[4]

4. **There Was No Conflict of Interest.**

Mr. Donnelly's November 23rd e-mail does not identify any specific legal or ethical standards that may be implicated by the outside activities of an NIH doctor.[5] At your suggestion, we have reviewed the CFR, as well as various NIH ethics programs and speeches by Administrators. While not an exhaustive summary, the following issues appear pertinent:

(a) *Did Dr. Sunderland have a financial conflict of interest?*

A financial conflict of interest exists when a personal financial interest might compromise the judgment related to conduct, interpretation, or dissemination of research or funding of research. We have reviewed the circumstances by which Dr. Sunderland interacted with Pfizer and the reasons for which he received compensation. Certainly, none of his lectures improperly compromised any NIH duty or obligation; and the same is true with regard to his consulting activities. We have reviewed the circumstances of the MTA and in that matter, rather than fostering a conflict of interest, Dr. Sunderland assiduously avoided one.

(b) *Did Dr. Sunderland grant Pfizer an unfair advantage?*

No. The MTA was the only instance where Pfizer received a direct benefit, and

[4] These quotes are drawn from an interview with Dr. Friedman, and this section was read to him on December 8, 2004, to make certain it is an accurate statement.

[5] As discussed in our telephone conversation, it is a strange procedure whereby "[t]he process for handling the results of all reviews in these matters is under development and will be communicated to all involved *at the conclusion* of NIH's reviews." (Emphasis added). It is made more so by the review of matters going back for five, six and sometimes seven years, a situation that would never be permitted in any legal proceeding. Both Dr. Sunderland's and NIH's files reflect a dearth of some materials, thereby making it difficult to reconstruct details of many of these events.

Dr. Sunderland removed himself from that decision making process, precisely to avoid a conflict. It bears repeating that the use of the samples by Pfizer was non-exclusive. In each of the approximately thirty other such CSF collaborations, an MTA was not executed. It was out of an extreme abundance of caution and concern about a possible conflict (or the appearance thereof) that Dr. Sunderland insisted that Pfizer negotiate an MTA. Furthermore, neither his speeches nor his consulting created unfair competitive advantages or showed Pfizer in a more favorable light, or caused any compromise of the NIH research.

(c) *Was the Pfizer income impermissible double dipping?*

Dr. Sunderland worked long hours at NIH, and there is no claim that he did not fully discharge his duties. Long hours and diligent commitment have been hallmarks of his work at NIH. Moreover, the Pfizer activity, i.e., lecturing and consulting, was precisely the type of "approvable" outside activity that doctors are allowed to do. To be sure, at different times, NIH approved Dr. Sunderland's requests for similar speaking and consulting on behalf of Pfizer.

(d) *Did Dr. Sunderland's activities for Pfizer have the appearance of a conflict of interest?*

This is a more difficult issue, and it brings us back to the word Mr. Donnelly uses at four points in his e-mail, namely "overlap." In some respects, it is a mischievous word because it suggests either impropriety or wrong-doing. But on closer examination, it helps clarify some of the problems that Dr. Sunderland and many of his colleagues are now confronting.

The fact is: every outside activity inevitably has an element of overlap. Dr. Sunderland is a preeminent scientist in the area of Alzheimer's research and geriatric psychiatry. If he is going to speak or consult, it will be in that area. No one wants to hear him speak on orthopedic injuries, infectious diseases or cancer research. Outside groups want him precisely for his expertise with Alzheimer's disease. There will always be some overlap. But that does not create an impermissible conflict. The conflict would come if the outside group paid Dr. Sunderland to advance its own interest to the exclusion of other groups or interests, or in some manner skewed or compromised the NIH research. That did not – and could not – occur, save possibly with regard to the MTA. But in that matter, Dr. Sunderland followed the exact rules necessary to avoid both a

conflict and the appearance of a conflict: he identified the possibility of a conflict; he was transparent with regard to his dealings; and he removed himself from any consideration of the decision to approve the MTA.

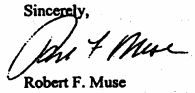
Conclusion

Throughout almost a quarter of a century at NIH, Dr. Sunderland has conducted himself in an honorable, professional and ethical manner. Not once in the past has there been a blemish on his record.[6] More specifically, no ethics allegation has been made at any time in these many years.

Let me conclude by again stating that Dr. Sunderland has committed no unethical acts. His failures have been in the context of not keeping and filing proper paperwork. In this regard, he was certainly not alone among NIH doctors and scientists. The investigation has exposed the indifference and difficulties relating to the filing and maintenance of records. Numerous doctors have been identified as having short-comings in this area. Yet we are confident that does not reflect a wide-spread ethical lapse among these doctors. There was instead indifference, lack of enforcement and administrative short-comings. NIH has recognized that the system was, indeed, broken. This was a failure that cuts across the whole spectrum of NIH, and involves doctors, scientists, OMA, the Administration, etc. By all accounts, changes are in the process of being established – for better or worse. This is a prerogative of the Director and others in leadership. But in the process of review it is important that individuals not be wrongly scarred. Dr. Sunderland can proudly stand on his record as a good, honest and compassionate doctor. He has well served NIH and its patients, and rightly stands as an honorable member of an elite corps of doctors. He had paid dearly for his failures. He is entitled to have his good name restored.

Please call if you have any questions. Thank you for your consideration of these remarks.

Sincerely,



Robert F. Muse

[6] Throughout this investigation, Dr. Sunderland has remained committed to the NIH and its mission, having avoided the frequent requests of the press. In fact, he has even continued to represent the NIH publicly when called upon. Just in the last month, he addressed a group of Congressional spouses for the NIMH, spoken at an annual luncheon for the Alzheimer's Association in Washington and presented an educational lecture for the NIH-wide post-[illegible] campus.

Tab 42

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August 31, 2004

Ms. Patricia D. Quast
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6011 Executive Boulevard, Suite 601
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CONFIDENTIAL

Re: Dr. Trey Sunderland

Dear Ms. Quast and Mr. Hainer:

Thank you for sending me a copy of your summary of Dr. Sunderland's interview. We have made modifications and added some points to help fill out the discussions we had at the interview on August 19, 2004.

We appreciate the efforts of the Office of Management Assessment to develop a full record of the relevant facts with respect to Dr. Sunderland's outside activities. In this letter we set forth some basic considerations that should be taken into account by the NIH with respect to this matter. A fair view of Dr. Sunderland's circumstances should reflect the following points:

- There was a widespread lack of attention among the NIH professional staff to the Forms 450 and 520. Dr. Sunderland, other scientists/doctors, and the administration in general did not give this subject the attention it is now receiving. During his interview, Dr. Sunderland explained the manner by which he completed the Forms 450 and 520. While he acknowledges that they were not complete, there was no effort at deception.

- Dr. Sunderland was open and obvious regarding his relationships with Pfizer and other pharmaceutical companies. He was not hiding these relationships, and many people at the NIH, including administrators, were fully aware of the fact that Dr. Sunderland both lectured and consulted for Pfizer.

- Dr. Sunderland had no conflict of interest in the discharge of his duties and functions at the NIH. For example, Dr. Sunderland went out of his way to ensure that his laboratory did not use Pfizer drugs in his research protocols. Also, his role in the Material Transfer Agreement (MTA) underscores the care that Dr. Sunderland took to avoid the appearance of a conflict.

1. Outside Activity Reporting At NIH

Various doctors and administrators have described outside activities reporting at NIH as a "system that was broken." The record on this point is overwhelming, and Dr. Sunderland's experience has to be viewed in the context of the overall atmosphere at the NIH with respect to the filing of Forms 450 and 520. While it is not an excuse for failing to properly file forms (something Dr. Sunderland readily acknowledges), this context provides a perspective for this entire matter.

From the doctors' point of view, little attention was given to these forms. The nature of Dr. Sunderland's work (like many others at the NIH) involves a mountain of paperwork: scientific data, research papers, speeches, fellowship programs, patient information, personnel matters, administrative activity, ordering supplies, etc. Dr. Sunderland deeply regrets that he did not pay more attention to the forms that are now the subject of this review. But this lack of attention to outside activity reporting does not justify an inference that he was hiding his outside activities or that a conflict of interest existed.

- The reporting problem was aggravated by an administrative/clerical situation that created a constant backlog of paperwork in Dr. Sunderland's office. Dr. Sunderland explained the circumstances by which he would fill out the Forms 450 and 520. Sometimes they would be completed by his secretary. Other times they would not be completed at all. We suspect that some of the relevant documents were simply lost in the administrative approval process. We showed you documents in which Dr. Sunderland's name was signed by his secretary well after the date of his outside activity. The secretarial problem was one that was shared by others at the NIH. To describe this state of affairs is not to avoid responsibility. It simply

underscores the general problem regarding the volume of paperwork and oftentimes inadequate administrative support services at the NIH.

- Dr. Sunderland has an explicit recollection of submitting separate Forms (520) for outside activity approval of a consulting and speaker's bureau relationship with Pfizer sometime in 1997. However, these forms were not in the file received from the NIH in early July. We are enclosing various Pfizer contracts on which Dr. Sunderland made the notations "Submitted" or "Copy – D," indicating that Dr. Sunderland submitted these to his secretary for inclusion in the approval process submission.[1] (Appendix 1). It is our assumption that these and other applications (i.e., speaker's bureau for the Lundbeck Institute, etc.) were either never fully completed and properly submitted or that they were lost further downstream in the administrative process.

- In March 2004, Dr. Sunderland received official approval through the NIH outside activity process for a consulting appearance on behalf of Pfizer. Additionally, within the administrative files obtained from the NIH were records reflecting approval of the 1997 APA lecture sponsored by Pfizer and other lectures where Pfizer was clearly the indirect sponsor. Thus, the suggestion that Dr. Sunderland had no outside activity approvals for his work with Pfizer is inaccurate.

2. **Dr. Sunderland Was Totally Open Regarding His Outside Activity**

Dr. Sunderland was open and obvious regarding every relationship he had with Pfizer and other pharmaceutical companies. During the interview, we showed you various brochures, pamphlets and written summaries, in which Dr. Sunderland's relationship with Pfizer was explicitly identified. (Appendix 2).

One of the most telling examples of Dr. Sunderland's disclosure of his relationship with Pfizer relates to the annual NIH-sponsored Foundation for Advanced Education in the Sciences Psychopharmacology course. On the first day of these lectures in November, 2001, November, 2002, and November, 2003, Dr. Sunderland directed the attendees' attention to the pharmaceutical company relationships for each

[1] At the time of Dr. Sunderland's interview, you requested that we provide you with those materials that could be located pertaining to his outside activities with Pfizer. As appendices, we are providing the available copies of the (1) Pfizer contracts; (2) excerpts from published disclosures at various presentations, including FABS; (3) examples of presenter rating survey results; and (4) a summary of Dr. Sunderland's outside activities by date and nature.

presenter. Dr. Sunderland pointed out his own relationships with Pfizer and other pharmaceutical companies. Several NIH administrators, including the director of the NIMH, were in attendance when Dr. Sunderland made these disclosures each year. He made these annual disclosures within a few days of his Form 450 filing.

In addition, whenever Dr. Sunderland made presentations at continuing medical education lectures or other symposia and meetings, his consulting and lecturing roles with Pfizer and other drug companies were clearly described in writing and/or announced at the start of the lecture (Appendix 2). For example:

- On March 14, 1999, Dr. Sunderland chaired a symposium entitled "Early Recognition and Treatment of Alzheimer's Disease." In the published program for this event, Dr. Sunderland disclosed that he is a speaker for Pfizer, Eisai, Lundbeck, Janssen and Lilly.

- On May 16, 1999, Dr. Sunderland gave a lecture at the 152nd APA Annual Meeting. In the published program, he disclosed that he is a consultant for Pfizer, Lundbeck, Eisai, SmithKline Beecham, Janssen, and Abbott.

- On March 14, 2000, Dr. Sunderland spoke at the 13th Annual American Association for Geriatric Psychiatry. In the published program, Dr. Sunderland disclosed that he is a consultant for Eisai, Janssen, Lundbeck, Pfizer, and Warner-Lambert.

- On May 14, 2000, Dr. Sunderland gave a lecture at the 153rd APA Annual Meeting. In the published program he disclosed that he is a speaker for Bayer, Eisai, Lundbeck, Parke-Davis, and Pfizer. This event was also sponsored by Pfizer.

- On January 22, 2002 and January 13, 2003, Dr. Sunderland disclosed his speaking and consulting relationships with Pfizer as well as relationships with Lundbeck, Janssen, Abbott, and Eisai to the University of California, San Diego Data Safety Monitoring Board.

What is the significance of these disclosures? At a minimum, they negate entirely the notion that Dr. Sunderland hid his relationship with Pfizer and other drug companies. The fact that he would note his relationships with these companies on an annual basis during the very week in which his Form 450 was submitted speaks volumes about the openness with which he treated these relationships.

3. Dr. Sunderland Had No Conflict Of Interest Regarding His Work

There was no conflict of interest between Dr. Sunderland's official duties at the NIH and his outside activities with Pfizer. Dr. Sunderland's primary focus at the NIH has been to try to understand the clinical course and biology of Alzheimer's disease. He conducts and oversees clinical research involving over a dozen NIH employees and hundreds of research subjects. The nature of this Alzheimer's research offered no realistic basis for any conflict of interest involving Pfizer. No Pfizer drug was used in any of the protocols or research endeavors in Dr. Sunderland's Branch; Dr. Sunderland had no grant authority that would have benefited Pfizer; and, Dr. Sunderland did not approve any Pfizer drugs. In a broader sense, Dr. Sunderland neither authorizes nor implements NIH policy regarding the pharmaceutical industry. His sole collaborative work with Pfizer in the research laboratory—the work covered by the MTA—involved the sharing of spinal fluid samples in return for analytical data on the fluids.

There is not a hint that, in his many speeches and lectures, Dr. Sunderland favored Pfizer or any other drug company. Much to the contrary, audience evaluations that follow his speeches have consistently identified Dr. Sunderland as the highest rated and least biased speaker at regional and national meetings. For example, Dr. Sunderland has been the highest rated speaker among all his colleagues at the last three annual FAES programs. Furthermore, at the most recent APA national meeting in New York, Dr. Sunderland's presentation received the highest score in the category: "provided an unbiased view." (Appendix 3) Indeed, it is his well recognized communication skills and lack of bias generally that allows Dr. Sunderland to be one of the most respected national authorities on Alzheimer's disease.

Dr. Sunderland's decision to encourage Pfizer and the NIH staff to establish an MTA for the spinal fluid transfer reflects the care that he took to avoid any potential concerns about his separate consulting work with Pfizer. Dr. Sunderland was approached by Dr. David Friedman, a Pfizer researcher, about a possible collaboration after he had read some of Dr. Sunderland's articles on Alzheimer's disease. Dr. Friedman was not aware that Dr. Sunderland also had an existing relationship with Pfizer when he approached Dr. Sunderland. Dr. Sunderland said that he would be very interested in a scientific collaboration, but raised a question about how to go forward without the appearance of a conflict. The idea of sharing spinal fluid in exchange for analytical data was not new; Dr. Sunderland has established more than two dozen such collaborations with other companies and academic institutions over the last twenty years without formal agreements of any kind. However, in light of separate lecturing and consulting work with Pfizer, Dr. Sunderland believed that some form of an

agreement should be developed (involving NIH administrators) which ultimately led to the MTA for this laboratory collaboration. There was no conflict between his consulting/lecturing and his clinical work at the NIH.

Conclusion

For close to 25 years, Trey Sunderland has brought honor and distinction to the National Institutes of Health. His reputation with colleagues throughout the profession has been sterling. His leading role in the effort to tackle Alzheimer's disease is well-recognized both nationally and internationally. His groundbreaking scientific work--and his effective communication of that work in a language that nonscientists can understand--represent the best that the NIH has to offer as a public institution.[2] It is Trey Sunderland and the doctors like him that make the NIH preeminent.

Now Dr. Sunderland finds himself in a strange world. His unblemished reputation has been challenged in a manner that defies logic. This singularly apolitical man has been placed in the middle of a political controversy as a Congressional process (however well-meaning in its purpose) created a cruel and unwarranted controversy. A headline was written and a reputation built over a quarter of a century was injured. This is wrong.

The relevant facts are now before the NIH in their entirety. The facts show that Dr. Sunderland made mistakes with regards to the Forms 450 and 520, and he has acknowledged those errors. But the facts also show that Dr. Sunderland's outside work for Pfizer was well known within the NIH; he never hid that relationship; and that there never was a conflict of interest--in any respect whatsoever--between his NIH work and what he did as a consultant and speaker for Pfizer. The facts show that the Congressional hearing and newspaper headlines that attacked this fine doctor's reputation were unfair, misleading and inappropriate.

It is time to put this matter to rest. We urge that NIH decide on appropriate action to reform the outside activities disclosure process at NIH and implement those changes fairly for all doctors and scientists who have not given the present process sufficiently close attention. But the NIH should also make clear that Dr. Sunderland did not engage in any conflicts of interest, and this determination should be made

[2] As an example of his communication skills, Dr. Sunderland presented the inaugural lecture in last year's Medicine for the Public series at the NIH (September 16, 2003). His talk, entitled "Alzheimer's Disease: Advances and Hope," was rebroadcast on C-Span multiple times over the following weeks.

promptly without the need for further interviews or legal submissions. Dr. Sunderland is entitled to have the record corrected.

Thank you for your cooperation and professionalism throughout this process. We hope and trust that the leaders of the NIH will now step forward to defend one of its finest professionals and end this needless controversy.

Sincerely,

Robert F. Muse

RFM/clg
Enclosures

MR. WHITFIELD. At this time, we have about 4 minutes left to cast two votes on the House floor, so Dr. Molchan, I will apologize to you, but we are going to take a recess here, go vote, and then we will be right back. We look forward to your testimony as soon as we return.

So thank you. We will get your opening statement when we get back.

[Recess]

MR. WHITFIELD. I would like to reconvene this hearing, and we had indicated that we would have an opening statement from Ms. Baldwin

when we resumed and she is not here, so at this time I would like to recognize Mr. Stearns of Florida for his opening statement.

MR. STEARNS. Thank you, Mr. Chairman. I certainly want to thank you for holding this hearing and your leadership here in prodding everyone to do this, today and tomorrow, surrounding the NIH policies on tissue samples. I also want to thank Dr. Molchan for testifying today and for the courage for coming to the subcommittee when you were troubled about this concern.

This hearing will ask if NIH has adequate policies in place to prevent diversion of human tissue samples for unauthorized purposes, and what is NIH policy on a chain of custody documenting human tissue samples from subject to each researcher that touches these samples, inside and out of NIH. Are we tracking the inventory or just willy-nilly sticking values on donations because this is what they are, a patient's literal blood, sweat, and tears, in the freezer with no tracking, no checks, and no balances. In other words, where is the oversight, where is the accountability here?

This hearing raises the question about conflicts of interest at NIH, researchers involved in outside research assignments in industry. At the hearing in the summer of 2004, I was one who questioned Dr. Sunderland about a lucrative outside financial contract he had with Pfizer, and that now has surfaced again in this hearing. The extramural research that NIH funds and is supposed to oversee so carefully sends positive rippling effects across organizations, academia, and facilities across the United States. For example, Alzheimer's disease, neuro-imaging initiative, ADNI, for which the doctor as the program director relies on software-supported imaging equipment developed and manufactured by Siemens, Phillips, and General Electric. The three primary companies that develop and manufacture imaging are providing for the imaging aspects of the project, while the company that manufactures magnetic resonant imaging, the MRI coils that these giants of diagnostic imaging use, make them in Gainesville, Florida, in my congressional district. So many different people depend on the integrity of NIH human tissue policies, from patients hoping and praying for a cure for their disease to biotech companies to small engineering firms.

Lastly, another question they have about this hearing is when the research subjects submitted a specimen CFS, did they consent to just a single study or did some at the NIH think it was a blanket consent for multiple uses and/or free reign over their spinal fluids for various research studies? In answer to that, I am troubled that it seems some at NIH did, in fact, handle these CFS specimens carelessly, sending them unauthorized to Pfizer without de-identifying them.

Again, this committee has passed my data bill, H.R. 4127, which applies only to industry, but it sounds like we need to consider Federal agencies handling of Social Security and other sensitive personal data as well.

Mr. Chairman, I thank you for exploring these issues and I yield back.

[The prepared statement of Hon. Cliff Stearns follows:]

PREPARED STATEMENT OF THE HON. CLIFF STEARNS, A REPRESENTATIVE IN CONGRESS FROM THE STATE OF FLORIDA

I want to thank Chairman Whitfield for holding this hearing today and tomorrow surrounding NIH policies on tissue samples. And Dr. Molchan, thank you for testifying today, and for your courage in coming to this Subcommittee when you were troubled.

This hearing will ask if NIH has adequate policies in place to prevent diversion of human tissue samples for unauthorized purposes? And, what is NIH's policy on a chain of custody, documenting human tissue samples from subject to each researcher that touches it, inside and outside of the NIH? Are we tracking the inventory, or just willy-nilly, sticking valued donations, because that is what they are, of patient's literal blood, sweat and tears, in the freezer with no tracking, no checks and balances? Where is the oversight, the accountability?

Also, this hearing raises questions about conflicts of interest of NIH researchers involved in outside research assignments in industry. At the hearing in the summer of 2004, I was one who questioned Dr. Sunderland about a lucrative outside financial contract he had with Pfizer, that now surfaces again in this hearing.

The extramural research that NIH funds, and is supposed to oversee so carefully, sends positive rippling effects across organizations, academia, and facilities across the nation. For example, the Alzheimer's Disease Neuroimaging Initiative (ADNI), for which Dr. Molchan is the program director, relies on software support and imaging equipment developed and manufactured by Siemens, Philips, and General Electric, the three primary companies that develop and manufacture imaging equipment. Well, the company that manufactures the magnetic resonance imaging (MRI) coils that these giants of diagnostic imaging use makes them in Gainesville, Florida: INVIVO Corporation. So, many different people depend upon the integrity of NIH's human tissue policies, from patients hoping, praying for a cure for their disease, to biotech companies, to small engineering firms.

Another question I have about this hearing is when the research subjects submitted a specimen of cerebrospinal fluid (CSF), did they consent to just a single study, Dr. Mochan's? Or did some at the NIH think that it was a blanket consent for multiple uses and/or free reign over their spinal fluid for various research studies?

And, advancing from that, I am troubled that it seems some at the NIH did in fact handle these CSF specimens carelessly, sending them, unauthorized, to Pfizer without de-identifying them! Again, this committee has passed my DATA bill, HR 4127, which applies only to industry, but it sounds like we need to consider federal agencies handling of Social Security numbers and other sensitive, personal data as well.
Thank you for exploring these issues.

MR. WHITFIELD. Thank you, Mr. Stearns.

At this time I recognize Ms. Baldwin from Wisconsin.

MS. BALDWIN. Thank you, Mr. Chairman.

The NIH is one of our national treasures. The intramural research done at NIH and the extramural research done in cooperation with outside partners is truly amazing and sometimes awe-inspiring. So much of today's most promising research involves human tissues. In order to translate biomedical discoveries into real improvements for people's medical care, we must first use human tissues to test a treatment or develop a new theory about how a disease develops. The work that is done with these human tissues holds the potential to do so much to advance human health.

I am distressed to hear about apparent lapses in accountability with regard to human tissue samples collected at the NIH. Why doesn't the NIH have a centralized system for tracking its tissue samples? Why is there no institute-wide inventory or accounting of what happens to these samples when a study ends? As our full committee and the Subcommittee on Health engage in discussions about health information technology, it seems like NIH could be a leader in this regard but at least in this arena, it certainly is not.

I think that what is most shocking to me is the carelessness and the way in which some at NIH appear to be treating such a precious commodity. While it is true that the samples are in freezers across the NIH and they might be vials of fluid or dishes of cells, it is important for us to remember that each of these samples originated in a person, and that person chose to share, chose to make a gift so that research could advance. At the very least, we must have practices in place that guarantee donor privacy and we need to ensure that donors are giving informed consent about how their donation will be used.

Lastly, a lot of these human tissues are non-renewable, and as I said earlier, they are a precious resource. We need to make sure that they are being used in the most appropriate and ethical way, not simply handed off to private companies.

Again, I am really shocked that some at the NIH would treat human tissues so carelessly, and that individual researchers would be given almost complete control over tissue samples without having to report to an impartial IRB, Institutional Review Board, like researchers at every academic research institution have to do.

I look forward to today's discussion, and I hope this hearing will lead us towards some answers. I want to extend a special thank you to today's witness, Dr. Molchan. I commend you for bringing information forward to this committee's attention.

Thank you, Mr. Chairman. I yield back.

MR. WHITFIELD. Thank you. At this time, I will recognize the full committee Chairman, Mr. Barton of Texas.

CHAIRMAN BARTON. Thank you, Mr. Chairman, for holding this hearing. As I said at the last set of oversight hearings on NIH, the hallmark of this committee has always been its oversight responsibility and its willingness and ability to hold agencies responsible under its jurisdiction that produces results and better government and better services for the American people.

When we held oversight hearings about the NIH ethics system several years ago, we found that there were weaknesses in the system at that time, and that those weaknesses were more severe than we had previously recognized. To his credit, Dr. Zerhouni, who had a ringside seat at those hearings, took the facts of the hearing seriously and changed and reformed the NIH ethics system.

Today, we are going to take a look at how the NIH protects its most precious assets, that is, the material that is at the core of NIH research mission, human tissue samples. Once again, after extensive investigation, on a bipartisan basis, I might add, we have found deeper concerns regarding human tissue samples at NIH than we first believed. We have found a lack of a centralized database, lack of oversight. This lack of a centralized database and lack of oversight could, and probably does, leave NIH laboratories vulnerable to the risks of theft and abuse. We know from previous investigations that the NIH has an inventory system, but NIH tells us that it has no centralized inventory system that could tell the NIH director how many vials of tissues are in freezers at a particular institute. It would really be a shame if we find out that the National Institutes of Health has more control over its paperclips and trashcans than it has over its human tissue samples.

The committee has investigated a case and found evidence of a serious breach of trust. This case is focused on Dr. Trey Sunderland, who is supposed to be a witness later today in these hearings. He is a very noted, and I might add, respected researcher in the field of Alzheimer's disease. I wish we were holding a hearing to congratulate him on some great discovery that he has made to cure or at least alleviate the hazards of Alzheimer's. Instead, we are going to have to discuss a way of how he used his position to use NIH spinal fluid samples to further his own undisclosed personal consulting. The information provided so far to the committee shows that a private corporation, Pfizer Corporation, paid Dr. Sunderland $285,000 during the 1998-2003 time period to consult on two projects involving spinal fluid samples that Dr. Sunderland had sent to Pfizer. During the same time period, Pfizer also paid Dr. Sunderland approximately $300,000 for lectures. These figures don't count an additional $200,000 for undisclosed activities with other companies. There is evidence that he advised his subordinate to conceal these consulting activities involving the samples. This is from an official

who chaired for 10 years the committee that reviews the ethics of conducting mental health research on human beings. This certainly appears to be a betrayal of the public trust that NIH so much stands for.

These hearings underscore the need to enact NIH reauthorization and reform legislation. The NIH director must have some baseline of information about NIH assets if we are going to gain new efficiencies and hopefully more effective ways to translate research into better healthcare. NIH reauthorization legislation is of the highest importance. Out of this investigation, deserving questions and concerns, we can use these hearings to make NIH stronger and better.

The National Institutes of Health is, indeed, a national treasure. It must be cherished, protected, nourished, and allowed to flourish. Today's hearing is a first step towards strengthening the public trust in NIH and preserving confidence in its integrity. I want to thank you, Mr. Chairman, and also the subcommittee Ranking Member, Mr. Stupak, for the bipartisanship nature of this investigation. I would also like to thank the Ranking Member of the full committee, Mr. Dingell of Michigan, for his support.

Finally, I want to say that I look forward to working with Dr. Zerhouni and others to improve in this area and to help NIH become better managed, and thus be able to deliver the results for the health of America that we so depend on NIH to do.

With that, Mr. Chairman, I yield back.

[The prepared statement of Hon. Joe Barton follows:]

PREPARED STATEMENT OF THE HON. JOE BARTON, CHAIRMAN, COMMITTEE ON ENERGY AND COMMERCE

Mr. Chairman, I am glad you are holding these hearings.

As I said at the last set of NIH oversight hearings, I hope one of the hallmarks of my chairmanship of the Energy and Commerce Committee will be holding agencies responsible and produce better government and better services and policies for the American people.

Two years ago, when we held oversight hearings about the NIH ethics concerns, we discovered that the weaknesses in the NIH system were severe. Dr. Zerhouni, the Director of NIH, had a ringside seat and realized that NIH's reputation was on the line. In light of our hearings, the NIH ethics system has been overhauled and reformed.

Today we look at how NIH protects precious assets, the human tissue samples that are at the core of the agency's research mission. Once again, after extensive investigation, we have found deeper concerns regarding human tissue samples at NIH than first believed. Incredibly, we have found a lack of a centralized database and oversight at NIH that leaves NIH labs vulnerable to theft and abuse. We know from previous investigations that NIH has an inventory system for its property, but NIH tells us it has no centralized inventory system that could tell the NIH Director how many vials of tissue are in freezers at a particular institute. It appears that the agency can account for its paper clips better than its invaluable research material.

The Committee's investigation has focused on one particularly brazen breach of trust. Dr. Trey Sunderland, a noted and respected researcher in the field of Alzheimer's disease, has discovered something that may have been even more important to him. He has discovered how to make money by using NIH's collection of spinal fluid samples in an undisclosed, personal consulting arrangement with a drug company. The information provided to the Committee is that Pfizer paid Dr. Sunderland $285,000 during the 1998-2003 time period to consult on two projects involving spinal fluid samples Dr. Sunderland sent to Pfizer. During this same time period, Pfizer also paid Dr. Sunderland around $300,000 for lectures. He also earned almost $200,000 more for undisclosed activities with other companies.

Dr. Sunderland might have been proud of his work, but he wasn't. There is evidence that he advised his subordinate to conceal consulting activities involving the samples. All this from an official who for 10 years chaired a committee that reviews the ethics of conducting mental health research on human beings. Mr. Chairman, this amounts to a breathtaking betrayal of the public trust and of NIH values.

These hearings underscore the need to enact NIH reauthorization legislation. The NIH Director must have some baseline of information about NIH assets. If we are going to gain new efficiencies and hopefully more effective ways to translate research into better healthcare, enacting NIH reauthorization legislation is of great importance.

Out of this investigation of disturbing questions and concerns, we can use these hearings to make NIH stronger. NIH is indeed a national treasure. It must be cherished. Today's hearings are a first step toward strengthening public trust in NIH research and preserving confidence in NIH's integrity.

I thank you and Mr. Stupak for the bipartisan investigation. I also thank Mr. Dingell for his support of this investigation. Finally, I look forward to working with Dr. Zerhouni and the leadership of NIH on this matter and helping NIH become better managed and better able to improve the health of the American people.

MR. WHITFIELD. Thank you, Chairman Barton.

At this time I recognize Mr. Walden of Oregon for his opening statement.

MR. WALDEN. Mr. Chairman, I am going to waive an opening statement this afternoon. Thank you.

MR. WHITFIELD. Thank you.

Mrs. Blackburn of Tennessee.

MRS. BLACKBURN. Mr. Chairman, I will waive and reserve my time for questions.

[Additional statement submitted for the record follows:]

PREPARED STATEMENT OF THE HON. DIANA DEGETTE, A REPRESENTATIVE IN CONGRESS FROM THE STATE OF COLORADO

Mr. Chairman, thank you for holding this important hearing. The issue is not just about the alleged wrongdoing of one research scientist at the National Institutes of Health (NIH). The larger issue we face is the systemic breakdown in how we protect patients who courageously agree to participate in clinical research. The NIH is the premiere biomedical research entity in the world. As a result, it is imperative that the research protocols used by the NIH be of the highest integrity. Clearly, that is currently not the case.

Let me first recognize our witness today, Dr. Susan Molchan, who brought this issue to the attention of the subcommittee. I believe we all owe you a debt of gratitude for coming forward.

Tomorrow we will hear from a number of witnesses from the NIH. The subcommittee's staff report raises many issues that our NIH witnesses must answer and I look forward to questioning the agency tomorrow about a number of my concerns.

Specifically, I am concerned that it appears as though the NIH cannot account properly for human tissue samples in its possession or for the data generated by the use of those samples in biomedical studies.

I would posit that the oversight function at NIH is in need of serious repair. Its investigatory ability is clearly inadequate when this Subcommittee has to uncover what the NIH cannot, even when it is trying. I sincerely hope that these hearings will assist the agency in straightening up the mess caused by its administrative shortcomings, just as our last hearings helped the NIH shore up its ethical standards.

When he was shown the extent of the ethical loopholes at his agency, NIH Director Dr. Zerhouni was very responsive. I have no doubt that he will be equally responsive in addressing the travesty created by the lack of accountability that this inquiry has uncovered.

All that said, what is most worrisome to me is the abuse of patients' trust. These people, victims of Alzheimer's Disease or their relatives, as well as some courageous individuals who have participated in the control groups, have submitted periodically for a decade or more to time consuming and painful spinal taps. They believed that the decisions regarding the use of these samples were made by the best scientific judgment in the country.

It is possible that only such an esteemed institution as the NIH could have enlisted these volunteers and convinced them to return again and again to give spinal fluid. Yet, we now know that some of these committed patients were never told that the experiments that used their samples had been aborted. Others were never given the results of completed efforts. Nobody was informed that samples left over from certain experiments were shipped from the NIH to private drug companies. Patients were not informed that there was a chance that their names, names that were supposed to be divorced from the samples in the event of them being used for research, could be inadvertently revealed. This did in fact occur when one of the Sunderland shipments to Pfizer revealed patient names to company researchers.

Mr. Chairman, these practices are unacceptable. Human subjects and their donated tissues simply must be protected as a first order of business by government researchers. The officials at NIH must be able to give ironclad assurances to these volunteers. To solicit cooperation and to take human tissue without proper protections in place is simply wrong, whether it is at the NIH or anywhere else.

Last week, I introduced H.R. 5578, the "Protection for Participants in Research Act of 2006" to provide clear and consistent protections for human subjects who take part in clinical trials, as well as providing clear guidelines to those conducting medical research. Specifically, this measure strengthens patients' rights to informed consent before subjecting to human subjects research. Perhaps this bill, given what we hear today and tomorrow from our panelists, could be used as a basis for further protecting human subjects, whether it is at the NIH, in universities, or at private companies.

I yield back the balance of my time.

MR. WHITFIELD. Thank you. That concludes our opening statements, and at this time, Dr. Molchan, we will call you as our first and only witness of the day.

Dr. Susan Molchan is the Program Director of the AD NeuroImaging Initiative, Neuroscience and Neuropsychology of the Aging program at the National Institute on Aging. Dr. Molchan, as you may or may not know, in the Oversight and Investigations Subcommittee, we do have, as a matter of policy, to take testimony under oath. I would ask you, do you have any objection to testifying under oath today?

DR. MOLCHAN. No, I don't. That is fine.

MR. WHITFIELD. Okay. Under the rules of the House and also the rules of the committee, you are entitled to be advised by legal counsel. Do you have legal counsel with you today?

DR. MOLCHAN. No, I don't.

MR. WHITFIELD. You are on your own?

DR. MOLCHAN. Yeah.

MR. WHITFIELD. If you would stand, I would like to swear you in.

[Witness sworn]

MR. WHITFIELD. Thank you. You are now under oath, Dr. Molchan, and at this time I recognize you for 5 minutes for your opening statement.

STATEMENT OF SUSAN MOLCHAN, M.D., PROGRAM DIRECTOR, AD NEUROIMAGING INITIATIVE, NEUROSCIENCE AND NEUROPSYCHOLOGY OF AGING PROGRAM, NATIONAL INSTITUTE ON AGING, NATIONAL INSTITUES OF HEALTH, U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES

DR. MOLCHAN. Thank you, Mr. Chairman. Mr. Chairman and members of the committee, my name is Dr. Susan Molchan from the National Institute on Aging at the NIH where I have worked since 2001 as the Program Director for clinical studies and Alzheimer's disease. I serve as a medical officer in the Commissioned Corps of the United States Public Health Service. Thank you for this opportunity to participate today. I have been asked to address my experience with human tissue samples at the National Institute of Mental Health where I worked for 9 years. I will address my experience specifically with one type of especially precious sample, spinal fluid, that I collected from a number of patients with Alzheimer's disease and volunteers in the early '90s.

As a young scientist at the NIMH, National Institute of Mental Health, I conceived and conducted a study that now has implications for Alzheimer's research. In the process of my research, I obtained a very valuable material, spinal fluid. These samples can be obtained only with the consent and understanding of each and every patient. As a doctor,

my first obligation is to advocate for patients who put their trust in me. Some of these patients had contributed their time and bodies to a number of my research studies and others at the NIMH. These good people are always ready to help and work on Alzheimer's in any way my colleagues and I asked.

While at NIMH, a redirection of the program occurred. New goals made it impossible for me to continue my work. Lack of support was intense and I was not encouraged to stay, so I went to work at the FDA for a few years until 2001, when I was recruited to my current position as a program officer at the National Institute on Aging where I work with Alzheimer's scientists throughout the country.

In 2004, some of these scientists, university scientists who are leaders of the National Institute of Aging's clinical trials consortium where I work now, which serves as the primary mechanism through which NIH funds studies on the treatment of Alzheimer's disease, proposed a study very similar to the one I had done while at the National Institute of Mental Health. Several of my very esteemed colleagues pressed me to obtain the samples I had collected. Such samples can be stored in freezers for years, and my colleagues and I had every reason to believe that they would still be available.

The head of the branch where I worked at NIMH located and sent a small subset of the spinal fluid samples to a university colleague for analysis. Twenty-five people had participated in the study, although I couldn't recall on how many I had collected spinal fluid for sure. Some got one spinal tap, others had gotten two. I did know I had collected it on more than the eight Alzheimer's patients and two volunteers on whose fluid was located. The individual responsible for the samples at the NIMH, Dr. Sunderland, e-mailed me that some of the samples had been lost in freezer thaw problems. A request to inspect the freezers to hopefully help find some samples was denied.

By the end of January 2005, intriguing data resulted from analyses of the spinal fluid samples that we were able to recover. Incomplete as it was, it contributed to the success of a grant proposal that shows promise in advancing knowledge on the mechanisms and treatment of Alzheimer's disease. Several colleagues agreed that the data from these samples were worth publishing in a scientific journal. These senior Alzheimer's researchers again pressed me for an answer as to why only a small amount of fluid was available, and only on a subset of the participants. This would need to be explained in any scientific submission of the data.

Since Congress had shown an interest in this matter, some progress has been made. I thank you for your interest in human tissue specimens that are so important to public health research.

Thank you.

[The prepared statement of Susan Molchan follows:]

PREPARED STATEMENT OF SUSAN MOLCHAN, M.D., PROGRAM DIRECTOR, AD NEUROIMAGING INITIATIVE, NEUROSCIENCE AND NEUROPSYCHOLOGY OF AGING PROGRAM, NATIONAL INSTITUTE ON AGING, NATIONAL INSTITUTES OF HEALTH, U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES

Mr. Chairman and Members of the Committee:

My name is Dr. Susan Molchan, from the National Institute on Aging (NIA) at the National Institutes of Health (NIH), where I have worked since 2001 as a program director for clinical studies on Alzheimer's disease. I serve as a medical officer in the U.S. Public Health Service. Thank you for this opportunity to participate today.

I have been asked to address my experience with human tissue samples at the National Institute of Mental Health (NIMH), where I worked for nine years. I will address my experience specifically with one type of especially precious sample—spinal fluid— that I collected from a number of patients with Alzheimer's disease (AD) and volunteers in the early 1990s.

As a young scientist at NIMH, I conceived and conducted a study that now has implications for AD research. In the process of my research, I obtained very valuable material—spinal fluid. These human samples can be obtained only with the consent and understanding of each and every patient. Those who participate in our research trust that their fluid specimens will be handled carefully. As scientists, we carefully document and store this material.

As a doctor, my very first obligation is to advocate for the well-being and intentions of the patients who put their trust in me. Some of these patients had contributed their time and bodies to a number of my research studies and others at the NIMH. These good people were always ready to help in work on AD in any way my colleagues and I asked.

While at NIMH, a redirection of the program occurred and the new goals made it impossible for me to continue my work. Lack of support was intense for this project and I was not encouraged to stay. I went to work at the FDA for a few years, until 2001, when I was recruited to my current position as a program officer at NIA, where I work with AD scientists throughout the country.

In 2004, the university scientists who are the leaders of the NIA's clinical trials consortium, which serves as the primary mechanism through which NIH funds studies on the treatment of AD, proposed a study very similar to the one I had done at the NIMH. Several of my esteemed colleagues pressed me to obtain the samples I had collected. Such samples can be stored in freezers for years, and my colleagues and I had every reason to believe that they would still be available.

As research on AD has progressed, the need for spinal fluid samples has increased, as they may shed light on treatment options for this increasingly prevalent and devastating disease. All available scientific resources are needed to fight AD.

The head of the branch where I had worked at NIMH located and sent a small subset (**one cc** per individual participant of the approximately **50 cc** that I'd collected from each) of the spinal fluid samples to a university colleague for analyses (tests that were covered on the consent form under which study participants allowed me to collect their samples).

Twenty-five people had participated in the study as documented on a Continuing Review memo to the NIMH IRB, dated July 1, 1993. Although I hadn't collected spinal fluid on all of them, I had collected it on more than the 8 AD patients and two volunteers on whom fluid was located. The individual responsible for the samples at the NIMH

emailed me that some of the samples had been lost in "freezer thaw problems." A request to inspect the freezers to hopefully find some samples was denied.

By the end of January, 2005 intriguing data resulted from analyses of the spinal fluid samples that we were able to recover. Incomplete as it was, it contributed to the success of a grant proposal that shows promise in advancing knowledge on the mechanisms and treatment of AD.

Several colleagues agreed the data from these samples were worth publishing in a scientific journal. These senior AD researchers pressed me for an answer as to why only a small amount of fluid was available, and on only a subset of the participants. This would need to be explained in any scientific submission of the data.

Since Congress has shown an interest in this matter, some progress has been made. I thank you for your interest in human tissue specimens that are so important to public health research.

MR. WHITFIELD. Dr. Molchan, thank you very much for cooperating with the committee and your willingness to come and testify.

How long were you actually at the National Institute of Mental Health?

DR. MOLCHAN. I worked at the National Institute of Mental Health for 9 years, from 1987 to 1996.

MR. WHITFIELD. Eighty-seven to '96, and was Dr. Sunderland there during that entire period?

DR. MOLCHAN. Yes, he was always my supervisor, yes.

MR. WHITFIELD. Okay, before I get to the lithium study, just to clarify here, when we talk about human tissue, and when we look at the specific testing that you were involved in, we are talking about spinal fluid?

DR. MOLCHAN. Yes.

MR. WHITFIELD. But when we talk about human tissue in general, we are talking about things like subcellular DNA, we are talking about tissues like skin.

DR. MOLCHAN. Anything that comes from body parts. Blood is a tissue, for example, spinal fluid is a tissue, as are the more solid--

MR. WHITFIELD. Okay.

DR. MOLCHAN. --components like skin.

MR. WHITFIELD. And fetal tissue, all of those things?

DR. MOLCHAN. Yes.

MR. WHITFIELD. Okay. Now, the lithium study that you were involved in, were you responsible for obtaining the spinal fluid for that study?

DR. MOLCHAN. I was responsible for obtaining most of the samples. The study was initiated by me and if it was going to get done, I was the one who had to do it. So I obtained most of the samples, though when I had to be somewhere else colleagues would step in and do so.

MR. WHITFIELD. And you said that the samples came from some Alzheimer's patients, as well as two patients who had no medical problems?

DR. MOLCHAN. The subset of the samples that were located last year, right. There were several Alzheimer's patients, eight Alzheimer's patients and two of the normal volunteers that had done the study.

MR. WHITFIELD. So when you are dealing with an Alzheimer's patient, how do you obtain their consent for a spinal tap?

DR. MOLCHAN. We did have procedures, clear procedures in place for that and they would co-sign, have a spouse or someone else responsible co-sign and understand.

MR. WHITFIELD. And what was the total volume of spinal fluid that you were able to collect?

DR. MOLCHAN. Generally we collected approximately 25 cc's or 25 milliliters, which is about five teaspoons.

MR. WHITFIELD. And that is from each person?

DR. MOLCHAN. That is from each person during one spinal tap, yes.

MR. WHITFIELD. And you had a total of nine or so patients that you obtained 25 cc's from?

DR. MOLCHAN. There were more than that, and what was important about this study that I had done is we were able to get two spinal taps on people, one while they were taking medication and the other when not on the medication so we could compare.

MR. WHITFIELD. Okay. So anyway, you used a small amount of this fluid for your research, and then you left the National Institute of Mental Health and went to FDA?

DR. MOLCHAN. Yes.

MR. WHITFIELD. And then when you went over to the National Institute of Aging, a similar study came up and so you thought well, it will be great to go back and get to this spinal fluid?

DR. MOLCHAN. Yes.

MR. WHITFIELD. And so you went to see Dr. Sunderland about the availability, I am assuming, or you talked to him or you made inquiry?

DR. MOLCHAN. Well, I inquired through one of my former NIMH collaborators originally who was still at the NIMH to inquire for me. I followed up later with Dr. Sunderland by e-mail, I believe.

MR. WHITFIELD. Because he was the person--

DR. MOLCHAN. Responsible--

MR. WHITFIELD. --responsible--

DR. MOLCHAN. --for them. Since he was the chief of the program there, the chief of the lab, yes.

MR. WHITFIELD. And so were you able to obtain samples from him?

DR. MOLCHAN. He did send samples from eight of the patients, eight of the Alzheimer's patients, two of the normals, but only half a cc from each spinal tap, half a cc out of 25 cc's. Now, I understand we didn't need a whole lot, but we would have liked a little more than a half of a cc, but when we asked for a little bit more or what happened to the rest of it, we just never got any good documentation of that.

MR. WHITFIELD. Okay. So you never did find out how much they had? Did they give you any explanation of where it was or anything?

DR. MOLCHAN. Just that some of it had been lost in freezer failures, freezer thaws, and that it has been a long time. So no, nothing solid, nothing that made sense, because I knew the recordkeeping where this was done was very careful. The spinal fluid is very important stuff for our research and Dr. Sunderland was always very careful about documenting how much we had and the research assistants would know in what freezers and what part of the--you know, whether it was collected late or early in the spinal tap. It is very detailed information.

MR. WHITFIELD. So as you sit here today, do you know for a fact what happened to it?

DR. MOLCHAN. No.

MR. WHITFIELD. You still do not know, okay.

DR. MOLCHAN. No.

MR. WHITFIELD. Okay. Now, you were at two institutes at NIH, and was there a protocol, a policy on the collecting, the storing, the tracing, the using of human tissue samples?

DR. MOLCHAN. Well, where I am now in the extramural program which deals with the university researchers, you know, helping to administrate and plan Alzheimer's research among the university community, whereas the intramural program does actual hands-on research, which I was in when I was in the National Institute of Mental Health. At that point, yeah, I just don't know. I wouldn't know about it. I think you are talking about the intramural program specifically, and I didn't know when I was there.

MR. WHITFIELD. But you obviously were surprised that you were not able to obtain any information about the availability of spinal fluid?

DR. MOLCHAN. Yes.

MR. WHITFIELD. And that you were not able to get the volume that you really needed to--

DR. MOLCHAN. Yes.

MR. WHITFIELD. --for your purposes?

DR. MOLCHAN. Yes, and I couldn't understand that.

MR. WHITFIELD. Now, did the people that you reported to at the National Institute of Aging, did you tell them about it and did they go to Dr. Sunderland about this issue, or was it just dropped?

DR. MOLCHAN. I tried to keep it within the National Institute of Mental Health, so I did mention it to my colleagues at Aging, but again, this was a separate time and place when I was at the NIMH. It is an intramural program working specifically with Dr. Sunderland, so while I let them know about it, I didn't expect or ask them to do anything. I told them I was following up with Dr. Insel and some other people.

MR. WHITFIELD. Now, at the time that you were at the Mental Health Institute, were you aware of scientists who had outside consulting agreements with--

DR. MOLCHAN. Yeah.

MR. WHITFIELD. So that was not anything unusual about having these consulting agreements?

DR. MOLCHAN. I don't have enough information to know how common or usual it was, but I know people did it and that there were ways to go about doing it.

MR. WHITFIELD. But you are not familiar with the disclosure requirements or anything like that, is that correct?

DR. MOLCHAN. For me with the intramural program at NIMH, these procedures have been evolving, these relationships between academia and industry, which I reiterate can be very positive if done in the right way. So I wasn't involved in any myself, I was busy enough with my work at the NIH so I never looked into the rules of it seriously.

MR. WHITFIELD. Well, from the knowledge and experience that you have had working there and your professional occupation as a physician and scientist, would you agree with the statement that the protocol in place for tracking and collecting and using human tissues leaves something to be desired at NIH or do you have enough information?

DR. MOLCHAN. Well, just from my experience, it apparently did. I mean, I hope this is an unusual--I think it is an unusual situation and otherwise, it is outside of my sphere of experience as to what an overall policy is there. I would have to confer with other people.

MR. WHITFIELD. Now, tell me, who is Karen Putnam?

DR. MOLCHAN. Karen Putnam, she worked with Dr. Sunderland for many years as a research assistant. She was, I believe--I don't know if she was a master's degree level. She helped with everything from doing neuropsychological testing on people to inputting data to helping organize data, just kind of keeping track of things in general. So she was a research assistant.

MR. WHITFIELD. And did you work with her on trying to obtain these samples?

DR. MOLCHAN. No. Karen, as far as I knew, had left the NIMH a few years ago, though she may have still been doing some consulting. I don't know. I really wasn't in touch with them.

MR. WHITFIELD. Okay.

My time is expired. Mr. Stupak?

MR. STUPAK. Thank you, Mr. Chairman. Doctor, thanks for appearing today.

You said Dr. Sunderland was your supervisor?

DR. MOLCHAN. Yes.

MR. STUPAK. When you drew these samples, these cerebral spinal fluid, did he supervise that withdrawing of these samples?

DR. MOLCHAN. No.

MR. STUPAK. Okay.

You indicated in a statement to the Chairman that sometimes your colleagues would step in and draw some of these samples for you, correct?

DR. MOLCHAN. Yes.

MR. STUPAK. Okay. Is there any way that Dr. Sunderland or someone else then could say that they sort of had ownership of these samples because they drew them?

DR. MOLCHAN. I have never heard of such a thing. From what I understood when I left and otherwise, the samples belonged to the Government. I don't think anybody would.

MR. STUPAK. So in this informed consent from these donors, did it identify the owner of the sample then being the NIH or NIMH?

DR. MOLCHAN. I would have to look at the language specifically, but again, that is such a broad question that we don't usually get into the details of. I guess most of us just assume that it belongs to the NIH, the government.

MR. STUPAK. You said you left NIMH and when you left, was your study supposed to continue or did it stop or what happened there?

DR. MOLCHAN. I assumed it would continue. When other doctors left, especially with clinical studies where patients had been involved, the studies were continued, the data analyzed and then written up and published.

MR. STUPAK. Sure.

DR. MOLCHAN. So I assumed that the people who were following on where my position was would continue it, but apparently that didn't happen.

MR. STUPAK. Do you know why your study stopped?

DR. MOLCHAN. I don't, no.

MR. STUPAK. Okay.

DR. MOLCHAN. Why it wasn't followed up, no.

MR. STUPAK. And you can't recite for us what the proper protocol or policy was on releasing any of these samples at NIMH then, the

samples you drew? Is there a certain procedure you have to follow before you release the samples? Say you release it to Pfizer--

DR. MOLCHAN. The only samples I used were with a scientific collaborator within the NIH and to look at the samples as stipulated in the consent form to look at the effects of this drug, on and off the drug, so that was the only experience I had. It was all within the NIH. Other than that, I drew the samples and put them in the freezer and the research assistants would catalog them.

MR. STUPAK. And before you would release it to collaborative effort to work with somebody else, whether academia or whatever it is, you would know how much of the sample was sent, how much was requested--

DR. MOLCHAN. Yes.

MR. STUPAK. --and the manner or method in which it was going to be used?

DR. MOLCHAN. Very much so. It was very specific. Depending on what you measure, you need certain amounts. I mean, sometimes you just need a tiny--you know, a drop, other times you might need as much as a few cc's, half a teaspoon.

MR. STUPAK. Okay. When you were at NIH or the National Institute of Mental Health and you went over to the Institute on Aging, was it necessary or were you required to get any new consent forms from any of the donors as these samples were now being used in a different part of the agency than which was originally drawn for?

DR. MOLCHAN. Well, again, the samples were collected in an intramural program. I am in the extramural program. I don't know if--I knew what we were interested in was covered in the consent form, because we wanted to look at the effects of the drug on the paired samples. And other than that we did academic circles, which in the past have been commonly done. People would make an agreement and I will send you so much and do such and such on it, and then send you the information, send you the data.

MR. STUPAK. If you can answer this one, if Dr. Sunderland teamed up with Pfizer to do some research outside of NIH for Pfizer's benefit, when a sample is given from a donor, it is for research purposes, so could the research being done by Pfizer meet the definition in that consent agreement, or is the focus of the consent agreement from the donor that the ownership control use is for the government and not for outside?

DR. MOLCHAN. Well, there are mechanisms to have a pharmaceutical company or a biotech company do an assay for you, and in exchange for doing the assay--I mean, some of these are very expensive to do, so it actually can be very helpful.

MR. STUPAK. So the issue here really is not how the sample might have been used, whether internally or externally, but the lack of knowledge or--

DR. MOLCHAN. Well, their samples--the way they are collected, the reason was to look at the effects of this drug on some of the proteins, some of the things we could measure in the spinal fluid. It is very specific to the actions of this drug, which has become of more interest recently in Alzheimer's research. So that was very specific.

MR. STUPAK. But was that for all of your samples you drew was for a very specific purpose type of research?

DR. MOLCHAN. Well, for each protocol that we did at the time, we collected, as you have gathered, a lot of spinal fluid, and for each protocol we had, as I recall, a separate consent form.

MR. STUPAK. Okay. I guess that is the best way to get a consent form is--okay.

So it would have been unusual then to have it go outside of NIH in the protocol that you had established to get this donation, if you will?

DR. MOLCHAN. In a general sense or from my study? I mean--

MR. STUPAK. The private gain companies in the mind of the donor, if you will. What is their expectation of how the sample is going to be used I guess is what I am trying to get at.

DR. MOLCHAN. Right. I would have to look at the exact wording on the consent form, but for the samples I drew, at least, they needed to be looked at in a paired way, on and off drug, to try to look at the effects of the drug.

MR. STUPAK. Sure, because you had a specific purpose that you were trying to test.

DR. MOLCHAN. Yes, and I recall that all protocol had a specific purpose. Again, the consent forms have been evolving and IRB policies, and from what I recall, we needed to get a specific consent form for each protocol that we did, because a number of the protocols did involve drawing spinal fluid.

MR. STUPAK. Sure, but if I am a donor, how many cc's would you take?

DR. MOLCHAN. About 25.

MR. STUPAK. Okay, 25. And I give permission and I give 25 cc's, and you used 5 cc's, would that consent then restrict the remaining 20 cc's from going elsewhere, or was it only for your study?

DR. MOLCHAN. As long as it was sent with the understanding of what was in the consent form and set up through NIH-approved mechanisms, that I think would be reasonable.

MR. STUPAK. Okay. I guess we will have to take a look at one of those consent forms.

If you have more than what you are using, I guess another thing I am trying to arrive at, though, the remainder then is it restricted within NIH or can it be used outside of NIH?

DR. MOLCHAN. Oh, no. In these things, we keep them in these big freezers which are very carefully regulated and backed up and controlled. We keep some of what we collect, whether it is blood or spinal fluid, in hopes that an interesting assay--something interesting we will want to measure in the future will come along. So these things literally can be stored sometimes for decades.

MR. STUPAK. Okay. In fact, in your testimony that you talk about the cerebral spinal fluid samples, which are highly valued, can be stored in freezers for years, and that you and your NIH colleagues had every reason to believe that they would still be available. So it is your understanding that the samples which NIH investigators may have an interest in are generally preserved and made available for possible research along the lines in which they were drawn from, extracted from?

DR. MOLCHAN. That is a bigger area of policy than I am involved with, and again, I think some of those policies are being evolved and worked on.

MR. STUPAK. Okay.

You also state in your testimony that "As research for Alzheimer's disease has progressed, the need for spinal fluid samples has increased as they may shed light on treatment options for this increasingly prevalent disease. All available scientific resources are indeed to fight AD." Could you elaborate further for the committee and for our understanding on how the loss of these samples and data could hamper further research or publications in the field of this research?

DR. MOLCHAN. Okay. Are we talking about my specific study samples?

MR. STUPAK. Yes.

DR. MOLCHAN. Since another study was being planned by this Alzheimer's clinical trial consortium that I work with now, it didn't make sense that I had done a similar study and we couldn't get information from it.

MR. STUPAK. The data, in other words?

DR. MOLCHAN. That we couldn't get data. I was able to give some of my experience as far the safety of the drug that we were using and everything in these Alzheimer's patients, and that was helpful, but it really would have been helpful to have more data on the effects on memory of what we were doing, as well as especially the spinal fluid because of being part of this new study that they want to do is to look at spinal fluid. It is a big part of helping us to try to understand what is going on in Alzheimer's disease. We can look at various measures in

spinal fluid, how those measures react to a drug, for example, tell us something about what is going on, what is going wrong in Alzheimer's.

MR. STUPAK. If you know, you took samples from 25 subjects, right?

DR. MOLCHAN. Yes.

MR. STUPAK. Of those 25 subjects, is there still partial of that 25 cc's left for all 25 or are some of them gone, some of them have a little remaining?

DR. MOLCHAN. That is what I could never ascertain. From what I understand, Dr. Sunderland sent the last of the samples to a collaborator of ours to measure something that the people planning this next study were interested in, that we were all interested in. I never got a handle on what happened to most of it.

MR. STUPAK. Thank you. Thank you, Mr. Chairman.

MR. WHITFIELD. Yes, sir. Dr. Burgess, I think we have about 8 minutes left in this vote. Would you like to start asking some questions, or would you prefer to just wait and come back after the next votes?

Why don't you go ahead and start, then?

MR. BURGESS. Very well. Again, thank you for being here.

I kind of know what a lumbar puncture is, but for the benefit of the uninitiated, maybe you could just quickly go through the procedure for us.

DR. MOLCHAN. Okay. They really, for one thing, really don't hurt that much, and they--

MR. BURGESS. Well, the Chairman said they took three hours. Now, it may take the Chairman three hours, but it shouldn't take the rest of us.

DR. MOLCHAN. He would definitely need more. We used to ask people--well--

MR. WHITFIELD. We could break now.

DR. MOLCHAN. Well, let me just go through the procedure. It is a lumbar puncture or a spinal tap, and we withdraw some of the fluid that is in the sac that surrounds the brain and the spinal cord, and that has certain proteins in it that we are interested in. So to withdraw some of this fluid, we introduce a needle in between a couple of vertebra in the lumbar spine in the back. People are usually on their side when doing this, and the area is numbed up with some local anesthetic. We insert the larger needle and withdraw about 25 cc's, which we allow to drip into however many--when I was doing it, about 10 tubes for use for various measurements.

MR. BURGESS. So it is a fairly invasive procedure?

DR. MOLCHAN. It is invasive. It is very safe and it contributes very much to our work, but yes, it is invasive. It is much more than drawing a blood sample.

MR. BURGESS. And in fact, 25 cc's is a fairly generous sample for someone who is used to doing them diagnostically.

DR. MOLCHAN. Yes.

MR. BURGESS. We would have normally obtained five to 10 cc's.

DR. MOLCHAN. That is right, when they did them, um-hum.

MR. BURGESS. And perhaps a little bit greater risk for things like headache and other sequella after--

DR. MOLCHAN. That is not well-documented and we actually followed the incidents of headache, and especially in the older people, it is actually quite unusual, but that is the biggest side effect is headache.

MR. BURGESS. Now, Mr. Stupak was asking about whether the patients involved in these trials were informed about the lithium trial being concluded or ended and then these samples being used in newer trials. To the best of your knowledge, there was no--that information wasn't given to the patients?

DR. MOLCHAN. No.

MR. BURGESS. Would that be unusual at NIH?

DR. MOLCHAN. Well, we had completed the data collection at least at that point. We had done all the spinal taps we were going to do and the next step would have been to work with some laboratories to measure what we were interested in. So as long as we were focusing on what was said in the consent form, measuring these paired samples on and off drug, then no, that would have been that. If it was going to be used for anything else, I am sure there were procedures that would have to be--you would have to go through.

MR. BURGESS. Now, you had samples on 25 individuals in this particular study. Can you give the committee any idea of how many tissue samples, which would include, of course, blood, urine, spinal fluid, other tissues, how many tissue samples are stored just in the intramural portion of the National Institute of Health at any given time?

DR. MOLCHAN. On an overall?

MR. BURGESS. Yeah, on an overall.

DR. MOLCHAN. Yeah, I have no idea.

MR. BURGESS. I know I don't either, but it has got to be a lot.

DR. MOLCHAN. Yeah, a lot is definitely what you are talking about of blood and urine specimens and cells. A lot.

MR. BURGESS. And yet, we have heard it mentioned several times that there should be a centralized databank, if you will, of all of the tissue stored at NIH. Do you think that is even technically feasible?

DR. MOLCHAN. Well, it depends how central. With our information technology now, and I know for some projects that we have in the university world that when we collect samples we do want to know what we are collecting and make them available to researchers to maximize their use. So these databases are starting to be built up. Again, it is a big coordinating effort using our information technology.

So they are underway and I don't know where they are in the intramural program with that at this point.

MR. BURGESS. But in the year 2006, that is just kind of beginning?

DR. MOLCHAN. Yes.

MR. BURGESS. In 1996, that probably would have been unheard of.

DR. MOLCHAN. Yes, most likely. Yes.

MR. BURGESS. The fact that there wasn't any centralized database for you to go to to find where your samples were, that wasn't necessarily unusual?

DR. MOLCHAN. No.

MR. BURGESS. Someone else doing research on diabetes that had blood sugar samples might have the same trouble?

DR. MOLCHAN. Yeah, I would be surprised, but yeah, not that I know of.

MR. BURGESS. Whose responsibility was it to keep those samples safe and retrievable during your tenure there and then after you left, where did that responsibility get assigned?

DR. MOLCHAN. From what I understand and from what I thought, it resided with each laboratory chief who was in charge of the certain projects under which the samples were collected.

MR. BURGESS. And that laboratory chief in your section would have been?

DR. MOLCHAN. Dr. Sunderland.

MR. BURGESS. Can you just tell us a little bit about the lithium study without giving away any trade secrets?

DR. MOLCHAN. Yes. There is, actually, one drug company doing a similar study now, too, but--

MR. BURGESS. I mean, lithium doesn't cure Alzheimer's.

DR. MOLCHAN. No, it does not. There has been some interesting data in the past few years showing that in cell studies and in mice studies that lithium seems to have some effects that hold off degeneration of neurons, including inhibiting the amyloid plaques and the neurofibrillary tangles. It is very interesting because lithium has never been thought of that way. So with these laboratory studies, it has become more of interest to use to see if we could give lithium and then see what happens, for example, in the spinal fluid to levels of amyloid and to levels

indicating the fibrillary tangles to see if we should target drug development along those lines.

MR. BURGESS. And that is important, because even though you are not curing Alzheimer's disease, even if you can slow down the course a little bit, that is important as well, isn't it?

DR. MOLCHAN. As far as the study we were doing, we were trying to find out more. We know lithium and when we use drugs in this way that they work under certain mechanisms, inhibit certain enzymes and so then we test what we can measure in the spinal fluid and from that, we can ascertain whether that enzyme, for example, is inhibited or not and would we want to work to dis-inhibit it to help Alzheimer's disease, things like that. So it is more mechanism.

MR. BURGESS. Do you know, do we know, does the committee know, is it available in our report or do you know the information about what were the samples used for, the samples that were diverted away from the NIH? Do we know what those were used for?

DR. MOLCHAN. I don't know.

MR. BURGESS. So then to the best of our knowledge, there hasn't been any published data about--

DR. MOLCHAN. Well, there was not after I left the institute, the study wasn't followed up, so no, there were no published data on the effects of lithium on these samples, which they were meant for.

MR. BURGESS. Were there any other studies of any type then done on these samples after they were diverted--

DR. MOLCHAN. That is what I don't know.

MR. BURGESS. --from your lab?

DR. MOLCHAN. I don't know.

MR. BURGESS. So we don't have that information?

DR. MOLCHAN. I don't have it. I don't know if anybody--

MR. BURGESS. Does anybody have that information?

DR. MOLCHAN. The committee staff may have some of it.

MR. WHITFIELD. We have some of that information which I can talk to you about as we go over--

MR. BURGESS. All right.

MR. WHITFIELD. Dr. Burgess, we have a minute to get over to vote, so when we come back we will recognize you for another 2 minutes.

MR. BURGESS. You are too kind, Mr. Chairman. I will delay further questions with that in mind.

[Recess]

MR. WHITFIELD. The hearing will resume, and at this time, I will recognize Dr. Burgess for his remaining two and a half minutes.

MR. BURGESS. Thank you, Mr. Chairman.

Dr. Molchan, did Dr. Sunderland ever talk to you about what happened to the samples or the research data from your study?

DR. MOLCHAN. Just in e-mails and phone calls. I got the information as related that the samples that he sent to our collaborating scientists was all that was left; that the rest was lost in freezer failures. He did indicate, I believe, that they had been used in--well, I would have to look at the records for sure, but from what I could get at the time, he gave me everything that was left. He mentioned some freezer thaw problems where samples were lost. As far as some data, he mentioned it is old data and everything--he seemed to be under the impression that it was published data, which it wasn't.

So I got an incomplete response as to what happened.

MR. BURGESS. And just to reiterate for the committee, why were you unable to complete the lithium study?

DR. MOLCHAN. I had to leave the NIMH. My time was up there and I had to leave, and at the time wanted to stay in the area. I was committed to stay in the Bethesda area and wanted to stay in the public health service, so I transferred to the FDA.

MR. BURGESS. Was there no one in the lab that you sort of signed out to and said this is what I am working on, the taxpayers have invested this much money in this lithium study. Would you please continue it?

DR. MOLCHAN. No.

MR. BURGESS. Would that be common to do that within a research lab if someone had reason to leave the lab?

DR. MOLCHAN. Well, when we were there I was on staff at the NIH clinical center, so I was no longer a fellow or anything, but again, the lab chief--it would have been unusual. That just wasn't part of the procedure. The lab chief had the responsibility for studies ultimately.

MR. BURGESS. Was the lithium study something that was assigned to you in the lab, or was this a concept that you had yourself that you--

DR. MOLCHAN. It was something that I wanted to do as an independent project. I had the idea based on some actual laboratory research that I had done years ago.

MR. BURGESS. But other people in the lab you discussed the lithium study with, had you convinced anyone that this was worthwhile research, or did everyone else--

DR. MOLCHAN. I thought so. I thought Dr. Sunderland, as well as at the time, the overall branch chief, and it went through, of course, the IRB committee of the NIMH, part of which debates whether it is a rational study to do, if it is worth doing, so yes.

MR. BURGESS. Does the committee need to be concerned that there are other studies that are just sort of dropped in mid-stride as people come in and come out of the NIH?

DR. MOLCHAN. Well, for clinical studies, I don't think there is any good--I mean, there are a lot of studies started by post-doctorals, perhaps, that some may not be followed up. When someone leaves, I guess many times they go to a university--to another laboratory and bring data with them, so that happens. And as far as an overall plan for what happens, that is beyond my experience.

MR. BURGESS. Well, you said in your testimony since Congress has shown an interest in this matter, some progress has been made. Can you elaborate on what you mean by "some progress"?

DR. MOLCHAN. Well, the NIH has instituted some trans-NIH policies on trying to better keep track of these samples, for one thing, and I was also able to get some additional data that I needed, just some basic demographic data on the subjects that we had the spinal fluid on so I can include that in a publication.

MR. BURGESS. Very well. Mr. Chairman, you know, I would just point out that we do talk about having some sort of centralized databank and I think that is a wonderful thing, but you know, in 1996, 1997, I don't know how feasible that was and in my experience in working in labs, I mean, you have got a refrigerator full of stuff and not everyone knows what all is contained therein and the importance thereof. I don't mean that that is right, if it sounds like the NIH is well on the way to remedying and rectifying that problem, but I just wonder about our ability to draw conclusions on a practice from 10 years ago when quite frankly, the computer database technology just may not have existed to keep track of what realistically may have been several million tissue specimens contained at the NIH.

I yield back.

MR. WHITFIELD. Thank you, Dr. Burgess, and of course, that is what we are going to be focused on as we move forward, and tomorrow we will have some other witnesses, including the Director of the National Institute of Mental Health.

At this time, I recognize Mrs. Blackburn for 10 minutes.

MRS. BLACKBURN. Thank you, Mr. Chairman. Dr. Molchan, thank you, and thank you for your patience with allowing us to go over and vote and then come back.

I will tell you that I am not a physician like Dr. Burgess, and not been involved in any of the research projects like he has, but I am very typical of a lot of Americans in that I have lost a loved one to Alzheimer's. And through that, have watched some of the research and some of the progress and some of the--I guess you would call them near-misses in your community. And I have found this really quite interesting to read through the materials for this hearing, and I appreciate very much your stepping forward, and working with us. You are making the

information aware, but I don't have to tell you, whether it is the NIH or any number of other Federal agencies, there is an arrogance that exists within the bureaucracy, a lack of respect that does exist for, I think, this body and for our oversight and for our desire to be certain that the taxpayers' money is appropriately spent. And I think it was quite appropriate that the Chairman of this committee, Mr. Barton, mentioned trust when he made his opening remarks, because it is a loss of trust in the NIH and how they spend their funds, and as we have the head in here, it is something that we are going to be discussing and visiting with him about.

A couple of questions I want to go back to, and I feel like I have got a page of notes here as you have talked and given your comments today. You mentioned that the comment was made you were told that you didn't find out exactly what had happened, that the loss of the samples was attributed to freezer loss and that nothing seemed to make sense. Now, who was it that told you that? Was it Dr. Sunderland or someone that worked with him?

DR. MOLCHAN. Dr. Sunderland, yes, in e-mails, yes.

MRS. BLACKBURN. Okay. So he himself--

DR. MOLCHAN. Yes.

MRS. BLACKBURN. --told you that, and you know that didn't seem right, because you know you are not going to lose that much through freezer burn, if you will--

DR. MOLCHAN. Correct.

MRS. BLACKBURN. --or--

DR. MOLCHAN. Or whatever reason. I just know how carefully we kept track of them when I was there.

MRS. BLACKBURN. Okay.

DR. MOLCHAN. And if there was a freezer failure, there would have been some documentation of that, dates and which samples were lost, and there is just nothing specific.

MRS. BLACKBURN. And I would imagine that the NIH with these freezers runs them from an operational standpoint that you have a generator backup so that you are never down, and you have got a flush point to move over in case you were to lose power, you would immediately go to a generator?

DR. MOLCHAN. I haven't dealt with these freezers for a long time, but they are quite technical and backed up and--

MRS. BLACKBURN. As I would imagine and we would expect.

DR. MOLCHAN. A record of the temperature every 24 hours and--

MRS. BLACKBURN. Okay. When I had stepped out of the room, I think that you were mentioning to our Chairman the material transfer

process. Were you giving a description of what that material transfer process was?

DR. MOLCHAN. I was probably explaining that I really--from my job back then at NIMH and my job now--I really haven't dealt with those, so I would have to--there is a whole staff at NIH now to help people deal with those, because it is getting more complex.

MRS. BLACKBURN. Okay. Now, Mr. Chairman, do we have something in writing that describes for us the process by which samples would be transferred within NIH and then to actually leave the jurisdiction of NIH? Do we have that in writing? Is there a document that we have received or should we request that from our witness?

MR. WHITFIELD. Just a minute. I will ask our counsel here.

MRS. BLACKBURN. And at the same time, do they have in writing a review process by which they would go back and review why a sample was requested?

MR. WHITFIELD. We have material transfer agreements. We have copies of that, and it is in the binder. It is Exhibit #2. Then we have Exhibit #38 is NIH technology transfer in U, an explanation of that, and then of course, tomorrow, as you know, we are going to have a number of panels here, three panels and everyone will be from NIH or has been. We will be able to get to that in more detail then.

MRS. BLACKBURN. Okay.

Dr. Molchan, I think you are familiar with those transfer processes, and would you agree that those and that the review, is it substantial, does it give you enough coverage, is there enough review if samples are requested?

DR. MOLCHAN. The samples of materials transfers?

MRS. BLACKBURN. Yes.

DR. MOLCHAN. I really have not dealt with them in any detail so I can't--

MRS. BLACKBURN. Okay.

Let me move on then. Dr. Sunderland in his relationship with Pfizer, would that be--from your vantage point, would you see that as being a normal or abnormal relationship for a researcher from NIH?

DR. MOLCHAN. Again, I don't have the details of the relationship, and haven't been in contact with Dr. Sunderland in years. I can't comment since I don't know.

MRS. BLACKBURN. Just from other researchers. And then also, is it a normal practice for NIH researchers who are working on a project to go and speak and be paid for the speeches for different pharmaceutical companies and then to be invited into relationships with those companies?

DR. MOLCHAN. As far as I know, it is not, and again, it never entered my area of activity or interest, especially since I was at the Food and Drug Administration, so I was totally out and divested in everything.

MRS. BLACKBURN. Okay. And then do you know if there is an oversight process and who would be involved in that process that would be checking the relationships with the NIH researchers?

DR. MOLCHAN. I don't know.

MRS. BLACKBURN. And you never had anyone come to you and question a relationship that you had?

DR. MOLCHAN. I haven't been involved in any relationships, you know, since I have been in the Government, especially since I went through the FDA.

MRS. BLACKBURN. Okay.

DR. MOLCHAN. It is just definitely not allowed there.

MRS. BLACKBURN. So while you were aware of others that were paid consulting fees--

DR. MOLCHAN. Yes.

MRS. BLACKBURN. --had consulting agreements, you had none of your own?

DR. MOLCHAN. No.

MRS. BLACKBURN. Okay. All right.

Let me ask you this, because I thought your comments to Dr. Burgess were interesting when you were talking about the lithium study and it just dissipated. How much money did you spend on that study through your process?

DR. MOLCHAN. Well, I didn't have a budget myself, and what it cost from the budget of the laboratory I was in, Dr. Sunderland's group and at that point, our branch chief, Dr. Murphy, they would have the numbers on that. I don't know what the cost was back then. I just don't, since I didn't have my own budget.

MRS. BLACKBURN. Okay.

Well, thank you, and Mr. Chairman, I will yield back.

MR. WHITFIELD. Thank you, Ms. Blackburn.

Mr. Molchan, Mr. Stupak in either his opening statement or questions, mentioned that around $6 million was the estimated cost of collecting these samples. Do you know how that figure was determined or calculated?

DR. MOLCHAN. He was talking, I think, of more samples than just involved in my study--

MR. WHITFIELD. Right.

DR. MOLCHAN. --so I don't know.

MR. WHITFIELD. Okay.

And now, what makes spinal fluid so valuable? Just the process of what you have to go through to get it?

DR. MOLCHAN. It is not the easiest thing to collect because you have to have special equipment, you have to have special storage for it. A lot of people, especially in this country--it is a common medical procedure done in many hospitals for many different reasons, and it is very safe, but still I guess the vision of having a needle placed into your back doesn't bode well for most people, so we have to convince people that it is worth it. The spinal fluid itself bathes the brain, some of the chemicals in the brain. It is the closest thing you can get to the brain without taking a piece of the brain.

MR. WHITFIELD. Absolutely.

I also want to ask unanimous consent that we enter into the record a form that is the consent to participate in a clinical research study, and this actually is a form that has you listed as one of the principal investigators. I don't think we have a copy of this for our record, so I would ask unanimous consent that we enter that into the record.

[The information follows:]

MEDICAL RECORD	CONSENT TO PARTICIPATE IN A CLINICAL RESEARCH STUDY • Adult Patient or • Parent, for Minor Patient

[redacted]TITUTE: NIMH

STUDY NUMBER 91-M-194 PRINCIPAL INVESTIGATOR: Susan Molchan, M.D.

STUDY TITLE: The Evaluation of Lithium Treatment in Dementia of the Alzheimer's Type, Major Depression, and Age-Matched Controls (Patients)

INTRODUCTION

We invite you (or your child) to take part in a research study at the National Institutes of Health. It is important that you read and understand several general principles that apply to all who take part in our studies: (a) taking part in the study is entirely voluntary; (b) personal benefit may not result from taking part in the study, but knowledge may be gained that will benefit others; (c) you may withdraw from the study at any time without penalty or loss of any benefits to which you are otherwise entitled. The nature of the study, the risks, inconveniences, discomforts, and other pertinent information about the study are discussed below. If you have personal, religious or ethical beliefs which you think might limit the types of medical treatment (for example, blood transfusions) that you would agree to receive (or would want your child to receive), you should discuss them fully with your NIH physicians (or appropriate members of the research team) before entering this study. You are urged to discuss any questions you have about this study with the staff members who explain it to you.

[redacted]

NATURE OF THE STUDY

The purpose of this study is to evaluate the effects of the medication lithium in patients who have memory problems thought to be due to Alzheimer's disease, as well as in older patients with major depression. Lithium is a commonly used medicine, and is actually a naturally occurring salt, which has been used by millions of people for decades, primarily for the treatment of mood disorders (severe depressions or mania). Depressed mood and anxiety are common symptoms in patients with Alzheimer's disease. The medications currently used to treat these symptoms may have serious side effects, especially in older people. A medicine like lithium, if it was of benefit to some symptoms in Alzheimer's disease, may be safer and tolerated better by some patients. In addition, in comparing the effects of lithium on some physiological or chemical measures obtained from blood samples patients and normal volunteers, we hope to obtain information on changes in hormones and brain chemicals that occur in Alzheimer's disease and depression, as well as clues as to the mechanism of action of lithium.

Acetylcholine is a brain chemical that serves as a "messenger" (neurotransmitter). Acetylcholine appears to be involved in normal memory functioning, and patients with Alzheimer's disease are known to have deficits in the acetylcholine system.

[redacted]

Pts

MEDICAL RECORD	CONTINUATION SHEET for either: NIH 2514-1, Consent to Participate in A Clinical Research Study NIH 2514-2, Minor Patient's Assent to Participate in A Clinical Research Study

STUDY NUMBER: 91-M-194 CONTINUATION: page 2 of 10 pages.

Lithium had been shown to increase acetylcholine in the brain, as well as other neurotransmitters that may be involved in memory function. Therefore, the effects of lithium on memory will also be tested.

Physostigmine is a medicine that slows the breakdown of acetylcholine, allowing higher levels of it to exist in the brain. Physostigmine has been shown in some studies to have modest positive effects on the memory performance of patients with Alzheimer's disease, so has been a much studied drug for this disease. It has also been shown to effect mood. We propose in this study to use physostigmine as a "drug probe", which means that after we administer a single dose of it, we will examine its acute effects on memory, mood, and on measures of hormones and neurotransmitters that will be obtained from blood samples collected. This may give us information on why physostigmine may be of benefit in some patients. Also, in comparing responses to physostigmine between patients with Alzheimer's disease and normal volunteers, we may learn something about what may be different in Alzheimer's disease and in depression.

Baseline Evaluation

A physical exam, blood tests, urinanalysis, EKG, and EEG will be done prior to participation in the protocol to confirm your state of general health. Blood will be withdrawn for later measurement of certain hormones and other biological substances. Blood taken from you over the course of the protocol would never exceed the amount that an individual would donate to a blood bank. You will also be asked to save your urine for a 24 hr period, again for later measurement of hormones and other body chemicals.

Clinical Trial

After being off all medicines for at least 3 weeks, you will be administered pink capsules, two times a day, that contain either lithium or a placebo ("sugar pill") for a period of 6 weeks. This will allow us to compare the effects of lithium to that of the placebo, and neither you nor the staff (except for the physician prescribing the capsules) will know whether you are taking lithium or placebo at any specific time. This is called the "double-blind" procedure. Drug effects using this procedure are more accurately assessed, as it helps to keep assessments more objective. This is also

why the lithium and the placebo will be given in identical-appearing capsules and why code numbers instead of drug names are used. A physician who is aware of what medication you are on will be available at all times through our inpatient unit.

During the period you are taking the capsules, you will be assessed periodically with memory tests and staff will record changes in the way you are feeling or behaving according to standardized assessment forms. Blood tests and urine collections will be done during both the lithium and placebo phases of the protocol. Additional small samples of blood will be removed to check blood levels of lithium and for other biochemical tests. For one of these tests, called the dexamethasone suppression test, a dose of a hormone will be given to you to take at bedtime, for one evening during each phase of the study. Blood will be withdrawn the next day at 8:00am and 4:00pm, for measurement of hormones in response to the hormone given the night prior. This test has been used for many years in medicine and psychiatry and no risks or side effects are associated with it.

Risks and Possible Side Effects

In some people lithium has been shown to cause temporary mild memory impairment. Someone who already has some memory impairment (as in Alzheimer's disease) may be especially susceptable to this side effect and to confusion after taking lithium. In addition, people with a history of a seizure disorder willl be excluded from this study; one reason for this is that lithium when given in combination with physostigmine at high doses causes seizures in rats. Seizures have not been reported from lithium in addition to physostigmine in humans. The most common side effects reported with lithium are nausea, feeling slowed down, skin rash, decreased concentration, and mild tremor. If you experience any bothersome side effects, the dose can be adjusted to reduce them or the the drug can be stopped entirely.

Any risk of stopping medication that you are on prior to the study will be explained. If this risk is more than minor, you will not be asked to stop the medication.

Two complications shave been reported in a small minority of patients who have taken lithium for long periods of time (months to years). One is a reversible slowing of the thyroid gland. The other is damage to the kidney which in some cases has been permanent.. Neither of these effects has been observed with lithium treatment for as brief as two weeks. Your thyroid and kidney function will be monitored during the study to assure their stability.

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MEDICAL RECORD | CONTINUATION SHEET for either:
NIH 2514-1, Consent to Participate In A Clinical Research Study
NIH 2514-2, Minor Patient's Assent to Participate In A Clinical Research Study

STUDY NUMBER: 91-M-194 CONTINUATION: page 4 of 10 pages.

CEREBROSPINAL FLUID EXAMINATION

Purpose

A great deal of research has been conducted here at the National Institute of Health and elsewhere in the past decade on chemicals found in the cerebrospinal fluid (CSF) of neurologically and psychiatrically ill patients. These chemicals are thought to be important in the normal and abnormal functioning of the brain. Studies of these chemicals significantly advance our knowledge of psychiatric and neurologic illness and of the actions of the medications used to treat these illnesses. For example, our studies suggest associations between levels of some of these chemicals and response to treatment in depression. In the present study, we would expect that measurement of these chemicals might help us better understand how lithium and physostigmine might act to help you or others.

The technique of lumbar puncture (LP) provides a method to study the CSF to learn some of what is going on in the brain biochemically without danger to the patient. The CSF is produced in the brain and collects various brain chemicals. The CSF then flows down the spinal column and collects in a sac in the lower part of the spine, four to six inches below where the spinal cord ends. We have attached a diagram of the anatomy of this region to demonstrate that direct damage to the spinal cord by the needle used is impossible, since the cord ends above where the needed is inserted. We would like you to participate in this procedure once during each phase (so twice altogether) of the protocol.

Procedure

You will be asked to follow a low monoamine diet for 3 days prior to the procedure; instructions for this will be given to you before the procedure; inpatients on 6W will already be on this diet. The LP will be performed in the morning, after a night's bedrest. You will lie on your side, your lower back will be cleaned with antiseptic, and a local anesthetic such as novocaine will be injected in order to temporarily numb a small area of skin. We then place a needle into the spinal fluid sac and allow approximately an ounce of CSF to drip into collection tubes. The needle is then removed and you are asked to lie on your abdomen for three hours to reduce

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the likelihood that you might develop a headache after this procedure. The LP should take only several minutes for insertion of the needle plus 5-15 minutes to allow the fluid to flow out one drop at a time. Most subjects experience only the minor discomfort of the pin prick used to administer the novocaine and compare it with the discomfort of having blood drawn from the arm. Others experience mild to moderate pain for a few minutes, similar to that experienced when an injection is received. The 15 minutes or so required for the fluid to flow out slowly is without pain or discomfort.

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MEDICAL RECORD	CONTINUATION SHEET for either: NIH 2514-1, Consent to Participate In A Clinical Research Study NIH 2514-2, Minor Patient's Assent to Participate In A Clinical Research Study

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Risks and Discomforts

The LP is a routine neurological procedure that is a common diagnostic procedure in every hospital. The only common discomforts are headache and mild backache. If it occurs, the slight backache resolves over one to two days. With the special bedrest procedure, three-quarters of all LPs (even less than that in older people) produce no headache. If a headache occurs, it generally is relieved by lying down. Most headaches last one to four days, although on rare occasions headaches can last more than a week. The rare prolonged headaches are thought to result from the continued leakage of CSF from the area of the LP. If the headache should last longer than one week, it would be possible to perform a "blood-patch." This involves the injection of a small amount of your blood into the region of the supposed leak, in an attempt to seal it. The blood-patch is usually effective in relieving the headache.

The other discomfort that can occur is a brief pain or tingling sensation in either leg. This is caused by brief stimulation of a nerve, and ends quickly with no further complications. On extremely rare occasions, a temporary weakness of the eye muscle that moves the eye to the side may develop, producing double vision. In all cases, this complication has been temporary, and normal vision is completely restored. Neurological problems could arise in patients taking anticoagulants ("blood thinners"), in patients who have an illness that slows blood clotting, or in patients who have a brain tumor or brain abscess. You will be screened thoroughly prior to the LP to insure that you do not have any of these medical problems.
Our own experience at the NIH involves over 6,000 LPs performed for research purposes; there have been no lasting complications.

____ I wish to participate in the cerebrospinal fluid examination.

____ I do not wish to participate in the cerebrospinal fluid exam.

_____
Signature

Prs

MEDICAL RECORD	CONTINUATION SHEET for either: NIH 2514-1, Consent to Participate In A Clinical Research Study NIH 2514-2, Minor Patient's Assent to Participate In A Clinical Research Study

STUDY NUMBER: 91-M-194 CONTINUATION: page 7 of 10 pages.

PHYSOSTIGMINE TEST

During both the lithium and placebo phases of the study, you will be asked to participate in the evaluation of the drug physostigmine, which has been used in many studies of memory, and is thought to work by inhibiting the breakdown of the neurotransmitter acetylcholine. In addition, on another day you will go through the same procedure but receive a placebo instead of physostigmine. Neither the staff doing the test with you or you will be aware of which day physostigmine and which day a placebo is administered, though this information will be available in the NIH pharmacy.

The purpose of this test is to evaluate changes that may occur in responses to after lithium treatment, as well as differences in responses between people with Alzheimer's disease or major depression and normal volunteers. Physostigmine affects acetylcholine, a brain chemical involved in memory processes, and possibly in the regulation of mood and the regulation of various hormones. The results of this study should tell us more about the chemical basis of certain behaviors and mood, and help us understand how lithium works.

Physostigmine Test

You will be asked not to eat or smoke for approximately 8 hours before each study day. During the test, you will sit either in a bed or a reclining chair for up to 4 hours during which time you will not be allowed to eat, drink, or smoke.

On the day of the test, a small plastic tube called a catheter will be placed in a vein in your arm. Prior to receiving physostigmine or a placebo, and at three points after, blood samples for hormone measurements will be obtained. You will receive a dose of glycopyrolate, a medicine used to counteract side effects of physostigmine, mainly nausea. After that you will receive a single small dose of physostigmine or of placebo (salt water) through the catheter in your arm. Three times during each study day, the examiner will ask you questions about how you are feeling. A short time after receiving either physostigmine or placebo, a staff member will do some memory tests with you. Your heart rhythm may be monitored during the procedure, using an EKG.

Pts

**EDICAL RECORD	CONTINUATION SHEET for either: NIH 2514-1, Consent to Participate In A Clinical Research Study NIH 2514-2, Minor Patient's Assent to Participate In A Clinical Research Study

STUDY NUMBER: 91-M-194 CONTINUATION: page 8 of 10 pages.

Possible Risks and Side Effects:

The placement of a small plastic tube (catheter) in your arm vein is associated with some discomfort, as when a blood test is taken. There is also the slight risk of a small bruise forming in the area of the catheter or a superficial skin infection. The total amount of blood samples taken during all three test days will be less than 150 ml (five ounces), which is less than 1/3 that taken during a routine blood donation.

The administration of glycopyrolate may be associated with dry mouth and sometimes slightly blurred vision. Side effects of physostigmine include nausea, excess salivation, sweating, dizziness, increased or decreased heart rate and blood pressure, feeling slowed down, and occasionally vomiting. Seizures have been reported to occur in animals given high doses of lithium in addition to high doses of physostigmine. We do not anticipate seizures as a side effect, but we are prepared to stop any seizure activity immediately if signs of it occur. Side effects will be minimized by the use of a small dose of physostigmine, as well as by prior administration of glycopyrolate. Any side effects experienced would be brief.

_____ I wish to participate in the physostigmine test.

_____ I do not wish to participate in the physostigmine test.

_____
(Signature)

part of your participation in this study, it will be necessary to test your blood for the presence of bodies to the Human Immunodeficiency Virus (HIV), the virus that causes Acquired Immune ciency Syndrome (AIDS). In order to perform the test, a small amount of blood (approximately 2 poons) will be withdrawn from one of your arms with a needle. You may experience some slight omfort at the needle entry site and there may be some bruising. In addition, there is a very small of your fainting or of infection at the needle entry site. If your test results are found to be tive, or if you are otherwise diagnosed as having AIDS, you should be aware of the following ical Center HIV Testing Policy:

Your physician will notify you promptly of the HIV test results.

Your physician and/or the Clinical Center HIV counselor will offer you, and any current and/or ongoing sexual partner(s) (spouses are generally considered to be current or ongoing sexual partners) or needle-sharing partner(s) you identify, information on the meaning of the test results and how to prevent the spread of the infection.

Because the virus may be transmitted in several ways, it is important that you inform sexual and/or needle-sharing partner(s) that any, or all, of them may have been exposed to the HIV virus and encourage them to be tested. If you request it, staff at the Clinical Center will assist yo[redacted]n notifying your partner(s) and arrange counseling for them through an HIV counselor.

[redacted]results of your HIV test and/or documentation of the diagnosis of AIDS will become a part of your Clinical Center medical record and, as such, will be protected from unauthorized disclosure by the Federal Privacy Act of 1974. In general, access to your medical record will be restricted to those health care professionals directly involved in your care or in the conduct of ongoing biomedical research, and information is not usually released to other third parties without your permission or that of your designated representative. However, there are some particular routine uses of such information of which you should be aware.

a. If you are unwilling or unable to notify your partner(s), the Clinical Center is responsible for attempting to contact and inform them of their possible exposure to the virus. Reasonable attempts will be made to protect your identity including withholding your name when notifying any partner(s) of their possible exposure. Some notification or counseling of current and/or ongoing partners may be carried out through arrangements with, or referral to, local public health agencies.

b. A summary of your care at the Clinical Center will be sent to the physician who referred you here for treatment.

c. The Clinical Center may report certain communicable diseases, including AIDS, to appropriate State and Federal government agencies.

h[redacted] any questions regarding the HIV testing or the information provided above, you are [redacted] to discuss them with your physician and/or a Clinical Center HIV counselor (496-8955).

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[redacted]AL RECORD	CONSENT TO PARTICIPATE IN A CLINICAL RESEARCH STUDY • Adult Patient or • Parent, for Minor Patient	continuation: page 10 of 10 pages

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OTHER PERTINENT INFORMATION

Confidentiality. When results of a study such as this are reported in medical journals,or at meetings, the identification of those taking part is withheld. Medical records of Clinical Center patients are maintained according to current legal requirements, and are made available for review, as required by the Food and Drug Administration or other authorized users, only under the guidelines established by the Federal Privacy Act.

Policy Regarding Research-Related Injuries. The Clinical Center will provide short-term medical care for any physical injury resulting from your participation in research here. Neither the Clinical Center nor the Federal government will provide long-term medical care or financial compensation for such injuries, except as may be provided through whatever remedies are normally available under law.

Payments. If you are a patient, you are not paid for taking part in NIH studies. Exceptions for volunteers will be guided by Clinical Center policies.

Problems or Questions. Should any problem or question arise with regard to this study, with regard to your rights as a participant in clinical research, or with regard to any research-related injury, you should contact the principal i[redacted]stigator, Dr. Susan Molchan, or these other staff members also involved in this study: [redacted]Drey Sunderland ; Dr. Husseini Manji * ; Dr. John Little ;
[redacted]ding 10, Room 3D41. Telephone: (301) 496-3421 OR
[redacted]ional Institutes of Health (301)496-2375
Bethesda, Maryland 20205 *496-2456

Consent Document. It is suggested that you retain a copy of this document for your later reference and personal records.

,COMPLETE APPROPRIATE ITEM BELOW, A or B:

Adult Patient's Consent.
I have read the explanation about this study and have been given the opportunity to discuss it and to ask questions. I hereby consent to take part in this study.

Signature of Adult Patient & Date Signed

B. Parent's Permission for Minor Patient.
I have read the explanation about this study and have been given the opportunity to discuss it and to ask questions. I hereby give permission for my child to take part in this study.
(Attach NIH 2514-2, Minor's Assent, if applicable.)

Signature of Parent(s) & Date Signed

(if other than parent, specify relationship)

[redacted] Signature of Investigator & Date Signed

Signature of Witness & Date Signed

IENT IDENTIFICATION

CONSENT TO PARTICIPATE IN A CLINICAL RESEARCH STUDY
• Adult Patient or • Parent, for Minor Patient

MR. WHITFIELD. At this time, Chairman Barton, would you like to ask some questions of this witness?

CHAIRMAN BARTON. Am I the last to question here?

MR. WHITFIELD. Yes, sir.

CHAIRMAN BARTON. Okay.

I have some questions. They are going to be a little bit more generic.

Does the administration at NIH share the committee's concern about lack of a centralized tracking system for human tissue sample collection and maintenance?

DR. MOLCHAN. You would have to--again, I am not at that level of policy and administration, so I don't--from what I have seen in e-mails, there is more and more interest in it in general in the research community.

CHAIRMAN BARTON. Well--

DR. MOLCHAN. The details of NIH, since that is not my purview--

CHAIRMAN BARTON. Well, let me rephrase the question.

DR. MOLCHAN. Yes.

CHAIRMAN BARTON. Do you share the concern?

DR. MOLCHAN. Based on my recent experience, understanding that these samples were collected several years ago, I think things are getting better, and I have seen movements towards policies and working groups being put in place to start to get some more consistent policies.

CHAIRMAN BARTON. All right.

What knowledge do you have of these spinal fluid samples: Have you been told what happened to the spinal fluid samples that you were so interested in that you couldn't get access to?

DR. MOLCHAN. I guess just from two sources. From Dr. Sunderland, which I just mentioned, that there weren't anymore left. Some of them were lost in freezer thaws, and then from what I understand, the committee found that some of them had gone to Pfizer from the NIMH.

CHAIRMAN BARTON. Well, 95 percent that according to committee staff briefings were unused, how many of those, in your opinion, have been misused or inappropriately sent outside of NIH?

DR. MOLCHAN. That is what I can't have any documentation of or try to ascertain but never got an answer, other than general answers that they are not there anymore, they were lost.

CHAIRMAN BARTON. You are okay with that?

DR. MOLCHAN. Well, I wasn't okay with that. That is how we ended up here.

CHAIRMAN BARTON. Do you have a solution?

DR. MOLCHAN. From my purview, I went through channels for a number of months and then expressed my concerns to the committee, and had done everything I felt I could do. I didn't think I was going to get an answer myself, and thought perhaps the committee might.

CHAIRMAN BARTON. You have hardly answered--I gave you a question right off the bat where you could say yes, we need a centralized system for monitoring and tracking our human tissue samples, and you basically told me that was outside your area of expertise; that you really didn't have a position on it.

DR. MOLCHAN. Well, it depends on a lot of details on that. I know that when we get into these policy things and at what level, it is a complex question and I think--

CHAIRMAN BARTON. It is not that complex.

DR. MOLCHAN. I mean, in a general sense--

CHAIRMAN BARTON. If you don't have a system in place--

DR. MOLCHAN. Right.

CHAIRMAN BARTON. --to back it across an agency, you are depending on pure faith that everybody--

DR. MOLCHAN. Of course, there are some systems in place. Again, how--and it is getting more consistent across the various institutes. I just don't know details of that since I am not--

CHAIRMAN BARTON. If you were in charge of the NIH, what would you change about the current system for human tissue sample collection, storage, and inventory, if you were in charge?

DR. MOLCHAN. Well, again, the NIH is a big place and I am just one tiny piece of it, and these samples came from 10 years ago. So yes, there needs to be careful documentation of who these samples were taken from and when and for what and the consents, where they go, what data results from them. Hopefully it will be shared among investigators, and I hope a lot of that is underway. I just can't, under oath, I guess I am just not comfortable going into too much detail because it is beyond my experience.

CHAIRMAN BARTON. So you have no recommendation?

DR. MOLCHAN. Well--

CHAIRMAN BARTON. What did you expect the committee to do when you contacted us?

DR. MOLCHAN. Well, I know that there has been some progress made, that there are trans-NIH--

CHAIRMAN BARTON. Is somebody at NIH pressuring you to hold back?

DR. MOLCHAN. No.

CHAIRMAN BARTON. Are you under any kind of threats? I have given you every opportunity to just absolutely tell us what you think needs to be changed, and you have resolutely refused. That is fine. You don't have to, but my gosh--

DR. MOLCHAN. I just don't know--

CHAIRMAN BARTON. --you are the person who came to us and said we have got a problem. You would think you would have some ideas about how to solve it, other than just say--

DR. MOLCHAN. Yes.

CHAIRMAN BARTON. --it is outside of my area of expertise.

DR. MOLCHAN. NIH is a big place and there are lots of different labs and different institutes, and I just have no idea of the policies in those places. It is outside of my purview, but yes, of course we need systems to track these things.

CHAIRMAN BARTON. How about some penalties if you abuse the tracking system?

DR. MOLCHAN. I would hope--

CHAIRMAN BARTON. Do you think it is appropriate that some of your spinal fluid samples went to Pfizer?

DR. MOLCHAN. Not unless they were used as indicated in the consent form and from what I have gathered, they were not, so no.

CHAIRMAN BARTON. Do you think Dr. Sunderland was truthful and honest with you when you inquired about those samples?

DR. MOLCHAN. Well, since I never got a complete answer and we all like to see data evidence, no, that is why I went further up the chain.

CHAIRMAN BARTON. All right. Do you believe at least said that he was not truthful and open with you?

DR. MOLCHAN. Yes.

CHAIRMAN BARTON. What would he have had to have done to have met your requirement that he didn't do?

DR. MOLCHAN. Just document, just tell us what happened to the rest of them, whether it was really in freezer failures--that large volume--again, from the careful documentation I knew went on in that laboratory on these types of things, I would have liked to see some documentation of what happened and when and there was just nothing like that.

CHAIRMAN BARTON. But to your knowledge today, there is not an acceptable accounting of those samples that were unused, is there?

DR. MOLCHAN. Correct.

CHAIRMAN BARTON. Are you okay with that?

DR. MOLCHAN. No, I have never been okay with it, and I have done what I can do--

CHAIRMAN BARTON. If you were Mr. Whitfield or Mr. Stupak, the Chairman and Ranking Member, would you insist on an accurate accounting of those samples?

DR. MOLCHAN. Yes.

CHAIRMAN BARTON. Okay.

DR. MOLCHAN. Yes.

CHAIRMAN BARTON. I guess, Mr. Chairman, that is all the questions I have.

MR. WHITFIELD. Thank you, Mr. Chairman.

Mr. Stupak, I understand you have a few additional questions?

MR. STUPAK. Yes. Doctor, if I may, to your right there is your consent form. You see it right there?

DR. MOLCHAN. Yes.

MR. STUPAK. And I note first that the form appears to be dated October of '84, so that form is already 22 years old. Have they updated the form since then, do you know?

DR. MOLCHAN. These are all 1984.

MR. STUPAK. Let me further identify, this is your evaluation of lithium treatment in dementia and Alzheimer's patients.

DR. MOLCHAN. That is right.

MR. STUPAK. This is your--

DR. MOLCHAN. And these are the details of the consent form that I asked them to sign, that is right.

MR. STUPAK. So you don't know if they have updated this consent form since then?

DR. MOLCHAN. The template I guess came from 1984, and I don't know.

MR. STUPAK. Okay. Let me ask you this, because I asked a lot of questions about consent form and things like that.

The consent forms only apply to your specific lithium study, so it raises at least two questions with me. Could the samples then be used for the consortium study on lithium use in Alzheimer's patients--or research, I should say, and the consortium, I mean with the University of Pittsburgh. Do you believe that based on this informed consent, those samples could be used with the consortium at the University of Pittsburgh?

DR. MOLCHAN. Since we were using samples on and off the drug of interest to see what the effects were, yes.

MR. STUPAK. Okay. Then how could such a specific consent form--because I do agree that it is pretty specific--cover transfer to Pfizer for a non-lithium study?

DR. MOLCHAN. It does not, from what I can see.

MR. STUPAK. And then there is no way you could bend that to make it cover--

DR. MOLCHAN. No.

MR. STUPAK. --Pfizer, unless they are doing something with lithium, right? That is your understanding?

DR. MOLCHAN. Yes.

MR. STUPAK. Okay.

DR. MOLCHAN. That is right. To look at the effects of the drug, yes.

MR. STUPAK. Correct, because you deal with a number of the neurotransmitters there, because--right? And you are looking to see how lithium acts on it?

DR. MOLCHAN. That is right, yes.

MR. STUPAK. Help me out here, acetocholene?

DR. MOLCHAN. Acetocholene.

MR. STUPAK. Acetocholene is a brain chemical that serves as a messenger or neuro-transmitter in the brain and lithium does affect that, correct?

DR. MOLCHAN. What we have been able to see in more Alzheimer's specific measures having to do with the amyloid that is deposited in the brain, things like that.

MR. STUPAK. Right, but that is spelled out pretty well in this study?

DR. MOLCHAN. But still we are looking at the effects of lithium on it to see if we should, again, go in the direction of a drug mechanism in the way that lithium works, if we should try to develop something similar with not so many side effects, for example.

MR. STUPAK. Thank you. I have nothing further, Mr. Chairman.

CHAIRMAN BARTON. Mr.--

MR. WHITFIELD. Yes, Mr. Chairman?

CHAIRMAN BARTON. I have just one or two more questions.

Dr. Sunderland, who has been subpoenaed to testify before this same subcommittee tomorrow, I believe, we were led to believe is going to plead the Fifth Amendment against self-incrimination, but he may not, but we are led to believe that. In your view, do you think that is an appropriate thing for him to do, in terms of the jurisdictional issues at NIH and responsibilities to be open and transparent in dealings with the public?

DR. MOLCHAN. I think NIH scientists should be as open and transparent with the public as possible, and from my experience, generally they are, so yes, they should be. And as far as him taking the Fifth, I don't know his full situation. I am not a lawyer, so I can't comment on that.

CHAIRMAN BARTON. Did he ever indicate to you when you were trying to get answers on these same questions that you should just mind your own business or bug off or it wasn't your responsibility anymore?

DR. MOLCHAN. Not from him. I got that impression from the NIMH director.

CHAIRMAN BARTON. And who is that person?

DR. MOLCHAN. Dr. Insel. That was from an e-mail where he indicated that I should, you know--Dr. Sunderland is occupied with plenty of other things right now. Please leave him alone.

CHAIRMAN BARTON. I understand how busy that fellow can be.

DR. MOLCHAN. Yeah.

CHAIRMAN BARTON. What is the general loss associated with freezer melting or whatever the technical term is? Would that normally be like one or two percent or 40 or 50 percent?

DR. MOLCHAN. It depends on the sample. I mean, in some of these freezers we have whole brains, for example, and it depends on what you are measuring and it depends on the sample.

CHAIRMAN BARTON. Well, in general, wouldn't you expect that high value human tissue samples, especially like spinal fluid that are difficult to obtain, that there would be some fairly elaborate--

DR. MOLCHAN. There are.

CHAIRMAN BARTON. --mechanisms and fail-safe--

DR. MOLCHAN. At the time I left the NIMH, there were quite elaborate systems of backup--

CHAIRMAN BARTON. You shouldn't have a high percentage of loss--

DR. MOLCHAN. Correct.

CHAIRMAN BARTON. --just from something like that?

DR. MOLCHAN. Right. There was backup and alarms, people would be called if there was a failure.

CHAIRMAN BARTON. Okay.

DR. MOLCHAN. Or if any temperature aberration, you know.

CHAIRMAN BARTON. Staff wants me to ask this question. What is the average cost per human subject in an Alzheimer's disease clinical trial? Average cost per human subject in an Alzheimer's disease clinical trial.

DR. MOLCHAN. For the Alzheimer's consortium that we deal with at the National Institute on Aging, we have been able to calculate that, and we have records. What did we say, about $12,000 per subject. Now, it depends on the length of the trial and how many tests you do, things like that, but on average for the trials we have done at NIA, it has been $12,000 per subject for what they call direct costs, and it is much more than that when you look at total costs when you are including the research infrastructure and data storage and analysis and other things involved most specifically with research.

CHAIRMAN BARTON. What percentage of that is the collection of spinal fluid, do you know?

DR. MOLCHAN. No.

CHAIRMAN BARTON. Just generally, would it be big percentages, little percentage?

DR. MOLCHAN. Well, when we collect spinal fluid--we haven't done it very routinely in studies in the past several years. We used to, and then we fell away from it, and now with the importance of it, we are including it in many more studies now. I just know, for example, for the lithium study that is being proposed for this consortium, the cost is estimated to be $17,000 per patient.

CHAIRMAN BARTON. Well, if Dr. Sunderland used some of these spinal fluid samples that we don't know what happened to, we know that

528 subjects were used in his Pfizer project, so based on your knowledge of the spinal fluid sample volume, how much of that missing spinal fluid would be needed for 528 subjects in this Pfizer project study?

DR. MOLCHAN. It would--again, how much spinal fluid would he need for--depend on, again, what he was measuring and lots of variables.

CHAIRMAN BARTON. But I mean, again, I am not asking you to be accurate to the milliliter.

DR. MOLCHAN. Yeah.

CHAIRMAN BARTON. But would it have taken half of the spinal fluid or--

DR. MOLCHAN. Oh, from a spinal tap?

CHAIRMAN BARTON. Yeah.

DR. MOLCHAN. Most of these assays take just a tiny amount, 2, 3 cc's, usually much less. Two or 3 cc's, say, out of the 25. Whether there are some tests out there that need more, I am not sure, but usually it is just a fraction of what we collect during a spinal tap, yes.

CHAIRMAN BARTON. I mean, but if he--and I am not saying that he did, okay, this is purely hypothetical. If he totally used these spinal fluid samples that are unaccounted for for this 538 subject project at Pfizer, would that have consumed one-third, one-fourth, one-fifth--

DR. MOLCHAN. I don't know, since I don't know all of his projects that he was doing with Pfizer.

CHAIRMAN BARTON. But it would take at least 3 cc's per subject?

DR. MOLCHAN. I would think, yes.

CHAIRMAN BARTON. When you take a spinal tap from an individual, how much fluid do you get out of that?

DR. MOLCHAN. Generally around 25 cc's.

CHAIRMAN BARTON. So it would take at least one-eighth.

DR. MOLCHAN. It is possible, yes.

CHAIRMAN BARTON. Just mathematically we would say--

DR. MOLCHAN. Yes.

CHAIRMAN BARTON. --he used an eighth of--that would be a fair--

DR. MOLCHAN. That is a fair estimate.

CHAIRMAN BARTON. --guess?

DR. MOLCHAN. Yeah, you don't like to put all your spinal fluid in one place, I hope, or send it to one collaborator, and you often want to keep specimens like that that are non-renewable on reserve for future interesting possibilities.

CHAIRMAN BARTON. Okay.

MR. STUPAK. Mr. Chairman, if I may?

CHAIRMAN BARTON. Sure.

MR. STUPAK. In the type of research that Pfizer was doing, I understand it is proteomics?

DR. MOLCHAN. Proteomics, yes, looking at--

MR. STUPAK. Does that take more fluid than a normal--

DR. MOLCHAN. That is what I--since I am not a laboratory assay person, I think some of those take a little more, maybe a few cc's, but I don't know really details of which proteins they are measuring, so I don't know.

MR. STUPAK. But it is fair to say in this type of study or research you are conducting, they would have needed more than normal of the fluid?

DR. MOLCHAN. More than normal as opposed to--

MR. STUPAK. In the other testing, compared to the lithium test.

DR. MOLCHAN. I think they do need--from what I understand, you need a fairly large volume compared to measuring some other things that were routinely measured.

CHAIRMAN BARTON. Pilfered.

MR. STUPAK. Thank you. Yield back to the Chairman.

CHAIRMAN BARTON. My final question. I asked you earlier what the cost per subject, and you said between $12,000 and $17,000. We really didn't get a good estimate if you know what the spinal fluid cost of that was, but let us assume that it is one-eighth. That would be about $1,500 per subject times 528 subjects, that is close to three-quarters of a million dollars that was used inappropriately.

DR. MOLCHAN. Well, the 538 came from a number of different protocols, the 538, and I don't know what was in all those consent forms, for one thing.

CHAIRMAN BARTON. If three-quarters of a million dollars of tissue samples were used in a privately funded study, somebody should sign off on that and the Government should be reimbursed for that cost. Do you agree with that?

DR. MOLCHAN. Yes, certainly.

CHAIRMAN BARTON. Okay. I yield back, Mr. Chairman.

MR. WHITFIELD. Thank you, Mr. Chairman.

That concludes this section of this hearing, and Dr. Molchan, we appreciate your being with us today.

Tomorrow, we will have some witnesses that hopefully will be able to be more specific on suggested protocols as we seek ways to guarantee the tracking of these human tissue samples. Tom Insel, who is the director of National Institute of Mental Health, is one of the witnesses. The Deputy Director for Intramural Research, Michael Gottsman, will be here, in addition to Dr. Trey Sunderland, Dr. Karen Putnam, and Dr. David Friedman.

So we will recess this hearing until tomorrow at 10:00 a.m., and Dr. Molchan, thank you again for being with us.

[Whereupon, at 4:52 p.m., the Subcommittee was recessed, to reconvene the next day at 10:00 a.m.]

HUMAN TISSUE SAMPLES: NIH RESEARCH POLICIES AND PRACTICES

WEDNESDAY, JUNE 14, 2006

HOUSE OF REPRESENTATIVES,
COMMITTEE ON ENERGY AND COMMERCE,
SUBCOMMITTEE ON OVERSIGHT AND INVESTIGATIONS,
Washington, DC.

The committee met, pursuant to notice, at 10:02 a.m., in Room 2322 of the Rayburn House Office Building, Hon. Ed Whitfield (Chairman) presiding.

Members present: Representatives Stearns, Bass, Ferguson, Burgess, Blackburn, Barton (ex officio), Stupak, DeGette, Inslee, and Whitfield.

Staff present: Mark Paoletta, Chief Counsel for Oversight and Investigations; Alan Slobodin, Deputy Chief Counsel for Oversight and Investigations; Mike Abraham, Legislative Clerk, Ryan Ambrose, Legislative Clerk; John Ford, Minority Counsel; Jessica McNiece, Minority Research Assistant; and William Garner, Minority Professional Staff Member.

MR. WHITFIELD. I would like to call this hearing to order.

Yesterday we had one panel of witnesses which was one witness, Dr. Susan Molchan, and today we are continuing this hearing on human tissue samples, NIH research policies and practices, and today we will have three panels of witnesses.

First of all, I want to thank all of you for joining us this morning. We made our opening statements yesterday so you are going to be very lucky. You don't have to hear a lot of opening statements today. And I would just make the comment that obviously all of us admire and respect the great work that is done at NIH. It is a premier research institution that is doing a tremendous job in trying to find cures and preventions for all sorts of diseases and it is a premier institution. I want to assure everyone today as the Chairman of this subcommittee, speaking for myself, I am not out to get anyone. But we do think it is essential that this institution with its reputation take all steps necessary to ensure the integrity of its research, particularly when people are donating samples. And we want to remove all possibilities of conflicts of interest or the appearance of conflict of interest. And so that is why we are particularly excited that you are here today and we look forward to the testimony from all of you.

On the first panel we have Dr. Thomas Insel, who is the Director of the National Institute of Mental Health at the National Institutes of Health, and we have Dr. David Friedman, who lives in Connecticut, so you will be the first two witnesses, and then in addition to Dr. Insel and Dr. Friedman, I guess accompanying you, Dr. Insel, we have Dr. Donald Rosenstein, who is the Acting Clinical Director at the National Institute of Mental Health. We have Mr. William Fitzsimmons, who is Executive Officer of the National Institute of Mental Health, and then we have Ms. Suzanne Winfield, who is the Technology Transfer Officer at the National Institute of Mental Health, but it is my understanding that Dr. Insel, you will be testifying and these three people will be here to assist if it is necessary. Is that correct?

DR. INSEL. That is correct.

MR. WHITFIELD. And Dr. Friedman, you will be testifying. As you know, this is an Oversight and Investigations Subcommittee hearing and it is our policy to take testimony under oath, and Dr. Insel, do you or Dr. Friedman have any difficulty testifying under oath today?

DR. INSEL. I do not.

MR. WHITFIELD. And under the rules of the House and the rules of the committee, you are entitled to legal counsel to advise you, and I would ask, do either of you have legal counsel with you today?

DR. INSEL. I do not.

MR. WHITFIELD. In just a minute I am going to swear you in, but before I do, I want to ask Mr. Stupak, the Ranking Member, if he would like to make any comments before we get started.

MR. STUPAK. No, Mr. Chairman.

[Witnesses sworn]

MR. WHITFIELD. You are now under oath, and Dr. Insel, we will call upon you for your 5 minute opening statement.

STATEMENTS OF THOMAS R. INSEL, M.D., DIRECTOR, NATIONAL INSTITUTE OF MENTAL HEALTH, NATIONAL INSTITUTES OF HEALTH, U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES; AND DAVID L. FRIEDMAN, PH.D.

DR. INSEL. Thank you very much, Mr. Chairman.

I have handed out some testimony which probably would go much more than 5 minutes. In thinking about this, I know you have many questions to ask. We have a lot that we would like to discuss with you, and I think rather than going through those five or six pages, if I can just provide you a very simple statement which I hope will be seen as in essence a statement of the principles that we are here for because I think

one of the things that we need to keep our eyes on here is what we are about and why it is so important that we protect the NIH mission.

As you mentioned, I am the Director of the National Institute of Mental Health, and this is an agency that has a large extramural component. Ninety percent of what we do is at universities and clinics and hospitals all around the country. We are here to focus on the intramural part, which is ten percent of our effort and it is the part that resides here in Bethesda, Maryland, and the part that we often think of as the jewel in the crown because it is a place for highly innovative, exciting science.

But I am also here as a physician and a scientist and I think you need to understand that I am absolutely committed to the mission of the NIH, which is to make discoveries to improve human health. For us, the clinical research which is part of what we do has to be understood as a real partnership and it can only be done because it is a partnership between clinical researchers who work as scientists and physicians and volunteers, research volunteers. These are people who may have illnesses, they may be actually healthy subjects, but they undergo painful and sometimes risky procedures to participate in this important mission that we have at the NIH.

We can only do this kind of work, it is just clear to all of us, if we understand that we are committed and the public understands that we are committed to minimizing risk, to protecting privacy and to using this information for the common good. That just has to be a fundamental, and as we think about this, I think you will agree that this whole enterprise that we are involved with really rests on trust. We can't do this without the public trust. We can't do this without your trust and we can't do this without trusting each other to some extent, trusting each other that we will do the right thing.

Whenever there is a conflict of interest or even a perceived conflict of interest, this trust is placed in peril and that is the situation that we are in this morning and as we talk about this individual case. There are many policies and there are various levels of review to preclude conflicts of interest and we will go through those I think over the course of the next few minutes, but basically it comes down to one simple principle, and this has to be seen for us as true north. That simple principle is that volunteers, their families, and the public must know that an NIH scientist is working for them and not for anyone else. We cannot allow a scientist or anyone else at NIH to trade his or her public role for private gain. It is very simple. That is the basis from which our ethics policy is built. Dr. Zerhouni sent out another message late last night to remind all NIH employees that that is a fundamental and that has to be understood. Violating this simple principle jeopardizes public trust and everything we

stand for at NIH and I will do everything, everything I can to ensure that this does not happen.

I look forward to your questions.

[The prepared statement of Thomas R. Insel, M.D. follows:]

PREPARED STATEMENT OF THOMAS R. INSEL, M.D., DIRECTOR, NATIONAL INSTITUTE OF MENTAL HEALTH, NATIONAL INSTITUTES OF HEALTH, U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES

Mr. Chairman and distinguished members of the Subcommittee: I am Dr. Thomas Insel, the Director of the National Institute of Mental Health (NIMH), the component of the National Institutes of Health (NIH), an agency of the Department of Health and Human Services (HHS), tasked with responsibility for developing improved methods of diagnosing, treating, and preventing mental disorders, including schizophrenia, autism, and mood and anxiety disorders.

To accomplish this mission, the President and the Congress have provided the NIMH a staff of over 700 employees and a budget of approximately $1.4 billion for Fiscal Year 2006. Nearly 90% of this budget, or almost $1.2 billion, is allocated to the support of biomedical research and research training activities through various grant, contract, and fellowship mechanisms at universities, hospitals, and clinics around the nation. The remaining $160 million per year is used to support a unique and critical intramural biomedical research program on the NIH campus in Bethesda, Maryland. This program was established to provide rapid responses to public health emergencies and to support an environment of innovation and creativity for biomedical discoveries. It is the operation of this intramural research program that is the focus of this hearing today.

First, I want to commend the Committee for its interest in NIH and the NIMH. As a public servant, I am well aware of my responsibilities to be a careful and vigilant steward of the public resources entrusted to my care. I know full well that you share my commitment on this point, and that you are working with all of us at the NIH to uphold the highest standards that can rightfully be expected by the public, whose support has enabled us to make remarkable strides in biomedical science. The Subcommittee has been working with NIH on several important issues and concerns that must be addressed, and I welcome the opportunity to cooperate with you as you continue to do so. I have already met with Subcommittee staff on three occasions. Based on the information that has been made available to me, I have taken action to improve our management of clinical samples. I am already taking corrective actions.

When I joined the NIMH in November 2002, I was impressed by the level of commitment to patients and families that was clearly so much a part of the culture of the Institute. NIH has been called the "crown jewel" of HHS, and I believe it is such a jewel, among other reasons, because of the dedication and skill of those who conduct research in our intramural program. It is because of them that we have made rapid progress against disabling diseases such as schizophrenia, bipolar illness, and depression. Our stakeholders, especially the families who struggle with these diseases, need us to do all in our power to ensure that science advances as rapidly as possible. At the same time, science—no matter how laudatory its objectives and results—must be conducted with the utmost emphasis on ethical standards, ensuring public trust and support. *This is not negotiable.*

To assure that the science performed at NIMH is of the highest quality and meets stringent ethical standards, there are policies and procedures for the conduct of clinical research, including the management of clinical samples and interactions with industry. We realize that science and public policies change over time and that our rules and procedures must be continually scrutinized for relevance and effectiveness. Although I

am confident in the high ethical standards held by our staff, we occasionally find serious problems can occur, as is the case in most large organizations. To the extent that problems result from systemic issues, I am working with the NIH leadership on institutional reforms.

At NIMH we recognize that rapid progress requires collaboration, including the exchange of clinical samples, such as blood or cerebrospinal fluid. As these samples are a non-renewable resource from patients involved in clinical studies, the management of these samples is an important aspect of our stewardship of the public trust. The following points may help the Committee understand our approach to this stewardship:

- Federal regulations require both Institutional Review Board (IRB) approval and informed consent, unless waived by the IRB, before a proposed study involving human subjects can begin.
- Samples derived from clinical studies conducted at the NIH are Government property under the responsibility and accountability of chief of the pertinent Laboratory or Branch. The use of these samples is part of our obligation to research volunteers, who are our partners in the discovery process.
- When a trainee or non-tenured investigator leaves the NIMH, the disposition of the clinical samples collected by that junior investigator remains the responsibility of the Laboratory/Branch chief. When the Laboratory/Branch chief leaves, the disposition of the clinical samples becomes the responsibility of the Institute's Scientific Director, who is also the director of the NIMH Division of Intramural Research Programs.
- Collaboration with non-government scientists in the private sector is encouraged as part of an intramural research scientist's official duty. This means that work with industry is done on official time and without non-government compensation. In the past, consultations with industry were permissible, subject to prior approval, if no Federal resources were used, no conflict or subject matter overlap with official duties was identified, and no other ethics concerns were present.
- Investigators with potential conflicts of interest are required to disclose these potential conflicts to the IRB as part of the review process. Like all executive branch employees, investigators who conduct clinical research generally may not participate in official matters in which they have a financial interest.
- The exchange of clinical samples may be an important aspect of collaboration. NIH is enhancing policies pertaining to the handling of human tissue samples and related intellectual property. At NIMH, I believe we have not done enough to ensure that all clinical samples leaving from or arriving at the Institute were adequately monitored. And, while the NIH has a variety of possible written mechanisms (including the Cooperative Research and Development Agreement (CRADA), the Material Transfer Agreement (MTA), and the Simple Letter Agreement(SLA)), these mechanisms have not been used uniformly within the NIMH.
- Current policies require that surplus tissue samples from completed studies need to be monitored through continuing IRB review if the samples are linked to patient identifiers. Although all of our intramural scientists engaged in clinical research are required to complete training in human subjects protections, I am concerned that NIMH investigators may not be uniformly aware of when the use of stored samples requires IRB review.

To address these concerns, I have done the following:

- On May 2, 2006, I called an intramural faculty meeting to review current policies and expectations for the handling of clinical samples.
- On May 26, 2006, the NIMH's Acting Clinical Director, Dr. Donald Rosenstein, and I sent a follow-up memo to all intramural scientists to remind them of the current policies and expectations. Specifically, we are requiring that all collaborations involving clinical samples be documented with a written agreement (e.g., CRADA, MTA, or SLA) and that these agreements be cross-referenced for potential conflicts of interest.
- Some of the clinical samples stored at the NIH are from studies that have been completed, meaning that they are no longer enrolling subjects and analyzing data. We are in the process of reviewing all collaborations using stored samples from both active and inactive studies by intramural clinical scientists to ensure that they have appropriate approval and documentation. For stored clinical samples of a completed study, we are requiring all investigators to have an active IRB-approved protocol with continuing review to permit monitoring of these samples.

It is important for the Subcommittee to realize that although standards and policies for clinical research and collaborations with the private sector have changed over time, certain rules of conduct have remained constant. NIH scientists have always been required to abide by the general principles of government service. It is a public trust requiring employees to place the public health over private gain. We need to be sure we provide NIH staff with the tools they need to maintain this high standard.

Mr. Chairman and members of the Subcommittee, thank you for taking the time to look into these issues at the NIH and the NIMH. We are very proud of the accomplishments that have been made by the NIH, and the fundamental and profound role the agency and its scientists have played in alleviating suffering from disease. We are in a unique position because not only do we have to answer to our primary stakeholders—our patients and their families—but we have to answer to you and to every member of the public who has entrusted us with their hard-earned dollars to carry out NIMH's profound yet straightforward mission: to reduce the enormous burden of mental illness and behavioral disorders through research on mind, brain, and behavior.

I will be pleased to answer any of your questions.

MR. WHITFIELD. Thank you, Dr. Insel. At this time we will recognize Dr. Friedman for his 5 minute opening statement.

DR. FRIEDMAN. Mr. Chairman, members of the committee, thank you for the opportunity to come before you today to discuss the facts relating to the use of cerebrospinal fluid and plasma samples in collaboration between Dr. Sunderland at the NIMH and Pfizer, Inc.

I have great respect for the work of this subcommittee and the process of scrutiny underlying this hearing as I believe they will serve to clarify issues and resolve questions about the process and the intent of these key studies.

I am appearing before you for several reasons. First, I have firsthand information regarding some of the scientific issues relating to the interaction between Pfizer and Dr. Sunderland. As an employee of Pfizer from 1995 to 2001, I initiated discussions between Dr. Sunderland and Pfizer regarding a possible scientific collaboration to search for and

evaluate possible biomarkers of Alzheimer's disease. Second, I have great respect for Dr. Sunderland as a scientist and clinician for his contributions to this important basic research. I also have great respect for each of the key contributors of these experiments including my former Pfizer colleagues and the NIMH staff and associates of Dr. Sunderland who participated in the effort.

I also recognize and respect the important contribution of the individual Alzheimer's patients and their respective families who contributed important CSF and plasma samples and underwent extensive testing over the past few decades resulting in the data and samples that are the subject of the discussion today.

Finally, I appear today in part because not doing so might be misinterpreted as not supporting the nature, process, and intent of this research effort.

I would like to make a few brief comments on the intent of this study as it relates to the issue of biomarkers. The information we sought in this experiment was essential to enable several medically important aspects of Alzheimer's disease treatment, a goal with enormous significance to patients, their families, and society as a whole. We sought to uncover new tools to enable the diagnosis and early detection of Alzheimer's disease. These tools are viewed as essential in the development of new therapeutics due to the current limitations in the unequivocal diagnosis of Alzheimer's disease. We also sought biomarkers for disease progression rate as well as biomarkers to stratify patients by specific disease stages. Last, we sought to identify markers of apparent normal individuals exhibiting no measurable cognitive defect who were at risk of developing Alzheimer's disease as a result of family history and/or genetic predisposition to the disease. This in turn might enable the treatment of cognitively normal yet affected individuals prior to their slow, progressive, debilitating decline.

It is important to recognize that these classes of markers serve several important roles. First, they facilitate and enable the proper clinical testing of potential Alzheimer's therapeutics under currently approved FDA guidelines. Second, they may enable and inform regarding the proper clinical diagnosis of patients by the general medical community and may facility the appropriate determination of medication for an individual's specific stage of disease. Finally, when these medications become available, these markers can also serve to enable physicians to individually monitor the response of their patients to ensure optimal and cost-effective treatment.

Given the magnitude of the societal burden of Alzheimer's disease now and in the near future, these are important tools to be uncovered and developed. Dr. Sunderland recognized the significance of biomarkers

and actively sought to identify biochemical markers as well as other types of markers in order to treat patients more effectively consistent with his role as an academic clinician at the NIMH. This was clearly obvious from his academic publications which in turn was the vehicle through which I as a Pfizer employee initially contacted him regarding an effort to uncover these important tools to assist in the diagnosis and treatment of Alzheimer's patients.

Thank you for the opportunity to testify, and I would be happy to answer any questions regarding these issues.

[The prepared statement of David L. Friedman, Ph.D. follows:]

THE PREPARED STATEMENT OF DAVID L. FRIEDMAN, PH.D.

Mr. Chairman and Members of the Subcommittee, thank you for the opportunity to come before you today to discuss the facts relating to the use of cerebrospinal fluid (CSF) and plasma samples in a collaboration between Dr. Sunderland, at the NIMH, and Pfizer Inc. I have great respect for the work of this Subcommittee and the process of scrutiny underlying this hearing, as I believe that it will serve to clarify issues and resolve questions about the process and intent of these key studies.

I am appearing before you for several reasons. First, I have first-hand information regarding some scientific issues relating to the interaction between Pfizer and Dr. Sunderland. As an employee of Pfizer, from 1995 to 2001, I initiated discussions between Dr. Sunderland and Pfizer regarding a possible scientific collaboration to search for and evaluate possible biomarkers of Alzheimer's disease.

Second, I have great respect for Dr. Sunderland as a scientist and clinician and for his contributions to this important basic research. I also have great respect for each of the key contributors to this experiment, including my former Pfizer colleagues, and the NIMH staff and associates of Dr. Sunderland who participated in this effort. I also recognize and respect the important contribution of the individual Alzheimer's patients and their respective families who contributed important CSF and plasma samples and underwent extensive testing over the past few decades, resulting in data and samples that are the subject of the discussion today.

Finally, I appear here today in part because not doing so might be misinterpreted as not supporting the nature, process, and intent of this research effort.

I would like to make a few brief comments on the intent of the study as it relates to the issue of biomarkers. The information we sought in this experiment was essential to enable several medically important aspects of treatment of Alzheimer's disease, a goal with enormous significance to patients, their families and to society as a whole. Specifically:

- We sought to uncover new tools to enable the diagnosis and early detection of Alzheimer's disease. These tools are viewed as essential in the development of new therapeutics due to the current limitations in the unequivocal diagnosis of Alzheimer's disease.
- We also sought to identify biomarkers for disease progression rate, essential to conduct cost-effective and efficient clinical drug trials given the heterogeneity of progression rates within this patient population.
- We also sought biomarkers to stratify patients by specific disease stages, knowing that various disease stages were likely to manifest differing components of the disease process and thus the potential to respond to different classes of therapeutics.

- Last, we sought to identify markers of apparently normal individuals, exhibiting no measurable cognitive defect, who were at risk of developing Alzheimer's disease as a result of family history and/or genetic predisposition to the disease. This in turn might enable the treatment of cognitively normal yet affected individuals prior to their slow, progressive, and debilitating decline.

It is important to recognize that these classes of markers serve *several* important roles.

- First, they may facilitate and enable the proper clinical testing of potential Alzheimer's therapeutics under currently approved FDA guidelines.
- Second, they may enable and inform regarding the proper clinical diagnosis of patients by the general medical community, and may facilitate the appropriate determination of medication for an individual's specific stage of the disease.
- Finally, when these medications become available, these markers can also serve to enable physicians to individually monitor the response of their patients to insure optimal and cost-effective treatment.

Given the magnitude of the societal burden of Alzheimer's disease now and in the near future, these are important tools to be uncovered and developed. Dr. Sunderland recognized the significance of biomarkers and actively sought to identify biochemical markers as well as other types of markers in order to treat patients more effectively, consistent with his role as an academic clinician at the NIMH. This was clearly obvious from his academic publications, which in turn was the vehicle through which I, as a Pfizer employee, initially contacted him regarding an effort to uncover these important tools to assist in the diagnosis and treatment of Alzheimer's patients.

Thank you for the opportunity to testify today. I would be happy to answer any questions you may have regarding this matter.

MR. WHITFIELD. Thank you, Dr. Friedman.

As you know, this subcommittee had a hearing in 2004 related to this overall issue and as a result of that, NIH and HHS both revisited and dramatically strengthened their ethics regulation, I believe in 2005. The question I would like to start off with, Dr. Insel, for you is, the period we are talking about relating to the spinal fluid transfer to Pfizer and Dr. Sunderland is roughly 1995 to 2001, in that general time frame, but at that time certainly the Institute encouraged collaboration with outside researchers. I mean, you can't do your job without doing that. So I am assuming that throughout the entire NIH, it was totally acceptable for scientists to have outside consulting agreements with private firms. Is that correct or is that not correct?

DR. INSEL. Just to clarify, Mr. Chairman, there was encouragement for collaboration with both academic and private scientists but what you have asked about in terms of consulting arrangements was seen as something different than collaboration, so consulting arrangements with anyone outside of the Federal government comes into a very different category. It could be approved but it would require approval and review.

MR. WHITFIELD. But it was not unusual for scientists to have outside consulting agreements?

DR. INSEL. It was not by any means unusual, but I just want to make sure we are clear about what we are talking about here. You could have both collaboration and you could have consulting agreements, but you couldn't have them with the same agent.

MR. WHITFIELD. With the same agent?

DR. INSEL. That is right.

MR. WHITFIELD. You mean with the same outside party or--is that what you are referring to?

DR. INSEL. That is correct.

MR. WHITFIELD. Okay. Now, before I get to Dr. Sunderland, let me ask you, any outside agreement that you had as a consultant, there would have to be disclosure of that agreement, I am assuming?

DR. INSEL. There is a whole system that would include prior approval--it would include review, approval, and then disclosure would be the minimal.

MR. WHITFIELD. So that protocol was already in place that you had to have the review, the approval and so forth, correct?

DR. INSEL. That protocol has been in place but I think as you know, beginning in 2005 there was first a moratorium on any outside activities, and in August of 2005 a new set of guidelines that now completely restrict outside activities and they are not permitted with either a pharmaceutical company or with biotech.

MR. WHITFIELD. Okay. Dr. Sunderland had executed a material transfer agreement with Pfizer in 1998. He also had the consulting agreement with Pfizer in 1998. At that time was that permissible under existing NIH policies?

DR. INSEL. It would not have been approved to have a consulting agreement and an outside activity with the same company at that time.

MR. WHITFIELD. Okay. So that would be a violation of the rules and regulations of the NIH at that time?

DR. INSEL. I wasn't here in 1998 but what I have been told is that that would not have been approved.

MR. WHITFIELD. Was it permissible under NIH policies in 1998 to provide human research samples from NIH labs to a drug company and have a consulting arrangement with that same drug company about those samples?

DR. INSEL. No, that is not--that again is the same issue. It is mixing collaboration and consulting, and that is where we get into this overlap between the scientific official duty of one of our researchers and their having some outside income from the same source.

MR. WHITFIELD. Right. Now, when we get into patent rights, could you briefly explain--with the caliber of the research that is going on and the new avenues that you are moving, it is not unusual to be involved in new patients. Could you briefly explain the policy of NIH as it relates to patent rights and the involvement of a scientist on your staff with an outside firm regarding patent rights?

DR. INSEL. Yes, of course. Ms. Winfield may be able to fill you in more from the Office of Technology Transfer's perspective because she does this for a living, but the opportunity to take discoveries and have them licensed is something that the NIH understands, appreciates, and encourages, and sometimes that can be done through collaborative activity. It is important for the subcommittee to realize that we are encouraging that kind of activity and we are encouraging it as official duty. We want people to work with industry to make discoveries and we want them to do that on government time. In the case where a discovery could be licensed, there is an opportunity to pursue that through the NIH. We have a technology transfer office that has a very well-developed set of guidelines about how that can be done.

MR. WHITFIELD. Well, I know that Dr. Sunderland, for example, assigned his patent rights and was listed on Pfizer's patent application as a co-inventor and I know he received no money for that, so was there anything wrong with that?

DR. INSEL. So--let me back up a moment. What you are telling me is that he was on a patent application that he received no money for. We have no record in the NIH of a patent application with Pfizer or anyone else from Dr. Sunderland.

MR. WHITFIELD. Okay. So you have no record of that?

DR. INSEL. So is that a problem for us, for any investigator? Let us take it away from this case, but to discover that someone has an application for a patent either with a private collaborator or without that relates to their official duty as a Federal employee and our agency doesn't know about it? Yes, that is a problem.

MR. WHITFIELD. Okay. Why is that a problem?

DR. INSEL. So what you are talking about is trying to license for potential commercial gain a discovery or an invention made through your Federal employment, and the Federal government has a stake in that. That is no different than if you as a Member of Congress decided to take something that was part of your official duty as a Congressional Representative and to create it as an invention and try to have it licensed on the side without telling anyone from Congress about that.

MR. WHITFIELD. Dr. Friedman, you were with Pfizer from 1995 to 2001?

DR. FRIEDMAN. Yes.

MR. WHITFIELD. And what were your responsibilities there?

DR. FRIEDMAN. I was part of an emerging biomarker group. Because of my doctorate in neuroscience, I had the responsibility for looking for alternative strategies for developing Alzheimer's therapeutics. I was also part of a committee to look for new technologies that were enabling in terms of identifying new biomarkers across a spectrum of disease areas.

MR. WHITFIELD. But the research was focused on Alzheimer's?

DR. FRIEDMAN. No, the research I was doing was focused on biomarkers for a number of neurological diseases including head trauma and depression.

MR. WHITFIELD. And when did you first have contact with Dr. Sunderland about obtaining the spinal fluid from NIH?

DR. FRIEDMAN. I first contacted Dr. Sunderland late in 1997, having spent a year on this committee looking for new technologies and realizing that it would be possible to do these experiments. We then sought a partner who had the experience and knowledge and access to samples that would make this project possible, so it was in the fall of 1997.

MR. WHITFIELD. And you all entered into a material transfer agreement with him to obtain these samples?

DR. FRIEDMAN. Pfizer did in 1998, yes.

MR. WHITFIELD. And at that time was there a consulting agreement in effect between Pfizer and Dr. Sunderland?

DR. FRIEDMAN. I wasn't part of any of the contracts or negotiations regarding the contracts. Having participated in these types of collaborations before, it was not unusual to have a consulting arrangement as part of a collaboration, but in no way was I part of those discussions.

MR. WHITFIELD. So from your personal knowledge, you were not aware of that?

DR. FRIEDMAN. Well, not only that, but it wasn't my role as a scientist.

MR. WHITFIELD. Right. How would you describe the success of the research that you conducted or that Pfizer was involved in relating to its efforts with NIH on this Alzheimer's project?

DR. FRIEDMAN. It is kind of a complicated question because there are multiple facets to that project, and so if you want me to speak in general about those?

MR. WHITFIELD. The one with the unknown biomarkers.

DR. FRIEDMAN. Okay. So that was the project we did in collaboration with an external partner, Oxford Glycoscience. That project where we are looking for unknown markers has in its technical

feasibly not been matched today. It was a huge effort to look for low-abundance markers in cerebrospinal fluid. It led to the identification of over 100 proteins that were likely stage-specific in terms of their release into the cerebrospinal fluid. The follow-up of that process is ongoing. I happen to know by looking at the patent literature that those patents have been updated the past couple of years so it looks as though Pfizer is actively pursuing not only the identification but the validation of those markers which takes several years, so I would view it as being highly successful.

MR. WHITFIELD. Right. I see my time has expired, so Mr. Stupak, I will recognize you for 10 minutes.

MR. STUPAK. Thank you, Mr. Chairman. Dr. Friedman, you indicated that you are familiar with the MTAs and the CRADAs that they use?

DR. FRIEDMAN. No, I indicated I wasn't familiar with them. I wasn't part of the process of--

MR. STUPAK. But I mean, outside of Dr. Sunderland, were you familiar with them?

DR. FRIEDMAN. No, I am actually familiar with doing collaborations with academic investigators as part of my role, not just at Pfizer but at other drug companies as well. It is not an unusual process, to say the least. What I indicated--

MR. STUPAK. Let me ask you this. I am looking at Exhibit #15 in the book there, and this is an e-mail and you are carbon-copied on it, and you talked about "pleased that this is working out well both on the scientists' side and on the tech transfer side. We do not need to have an MTA signed prior to CMC on March 12, Julie." And it sort of goes through this meeting, and according to our understanding, you were at this meeting on February 28 when you went to see Dr. Sunderland. Do you remember the meeting of February 20, 1998, when you went to meet--

DR. FRIEDMAN. In general I do.

MR. STUPAK. Okay. Do you remember seeing this e-mail?

DR. FRIEDMAN. I have seen the e-mail several times, once obviously back then but also subsequently during my prior visits to begin discussions about my role.

MR. STUPAK. Well, my concern is, in this e-mail it says, "In discussions regarding Pfizer's needs and Sunderland's needs, Trey indicated he was very happy with MTA arrangement plus consulting that Kathy Smith has been discussing. Trey was also very interested in publication in a reasonable timeframe and that he wanted to make sure that authorship would be based on scientific and intellectual contributions. We indicated agreement on both matters." It seems to me

that on February 20 from reading this e-mail and the whole of it, not just the part I quoted, that there were discussions about payment and things that Pfizer would receive from Dr. Sunderland. Is that correct?

DR. FRIEDMAN. Yes, it is correct. I was--

MR. STUPAK. Didn't you think that was unusual, that you would be paying a scientist at NIH--or NIMH--excuse me--for his samples and things like that?

DR. FRIEDMAN. First of all, this meeting was a mixture of both business and scientific people from Pfizer, so Kathy Monahan was part of the business end of the process.

MR. STUPAK. You were there and three other Pfizer scientists?

DR. FRIEDMAN. Yes. Correct. I was there because I had initially made contact with Dr. Sunderland and we had established a scientific relationship. We had even begun the discussion about the collaboration prior to--

MR. STUPAK. Yeah, but it says "take care of Pfizer's needs and Sunderland's needs."

DR. FRIEDMAN. Those comments were actually from Kathy Smith regarding her interpretation of how the discussions about future--

MR. STUPAK. You didn't think that was what happened at that meeting?

DR. FRIEDMAN. No, I didn't say that at all. I can't say clearly that at the time and even until recently, I don't know the difference between a CRADA and an MTA in terms of the implications.

MR. STUPAK. What did you understand Dr. Sunderland's need would be then?

DR. FRIEDMAN. I didn't try and interpret what his need would be.

MR. STUPAK. What were Pfizer's needs at the time of the February 20, 1998, meeting?

DR. FRIEDMAN. In a business sense, I don't know. From a scientific sense, we were looking for someone who had well-characterized samples. We were looking for someone who was an expert in the field of Alzheimer's disease because without the combination of those, the efforts that we would put forth would be worthless.

MR. STUPAK. Did you think it was odd that you would be paying for these samples?

DR. FRIEDMAN. I didn't--in no way did I interpret that we were paying for the samples. We were paying for the opportunity to have a collaboration with Dr. Sunderland and in no way did I know what the specifics of this type of--

MR. STUPAK. So you are saying all this money that Pfizer paid, it wasn't for the sample, it was for the opportunity to work with Dr. Sunderland?

DR. FRIEDMAN. That is my interpretation, yes.

MR. STUPAK. Really?

DR. FRIEDMAN. Exactly.

MR. STUPAK. Were samples just thrown in then as good faith or something?

DR. FRIEDMAN. I don't think you can put a value on the samples. In spite of the discussion yesterday, I think any attempt to try and do that type of analysis is impossible.

MR. STUPAK. The most important thing was really the samples, weren't they?

DR. FRIEDMAN. No, the samples are actually useless without the clinical information associated with them. They were--

MR. STUPAK. Couldn't you ake the samples and have them analyzed and have other labs take a look at it depending on what you are trying to do with those samples?

DR. FRIEDMAN. Alzheimer's--

MR. STUPAK. There was a great benefit to Pfizer, wasn't there?

DR. FRIEDMAN. Alzheimer's is a very complex disease. Knowing what type of patients these came from is almost as valuable as knowing--

MR. STUPAK. Well, not just the patients but also the patient's extended family, blood relatives, some who had--

DR. FRIEDMAN. Absolutely. All of that data is critical to interpret the biochemical measures that we were acquiring as part of this collaboration. We would never have ventured into this without having that complete set of information because otherwise it would be uninterpretable.

MR. STUPAK. Do you know if Pfizer had other MTAs or CRADAs with NIH?

DR. FRIEDMAN. With NIH?

MR. STUPAK. Yes.

DR. FRIEDMAN. I wasn't aware, but I wouldn't be surprised if they did.

MR. STUPAK. But the samples and the clinical data were transferred under the MTA. In fact, Pfizer was upset because they were transferred in June and they didn't get the data until August, right?

DR. FRIEDMAN. I wouldn't characterize it as Pfizer being upset. There were probably members of this project who were more concerned with timelines that were upset about the timing of it but the scientists as part of the project recognized that we would need 6 months at least to acquire that type of biochemical data prior to integrating it with the clinical data to interpret it.

MR. STUPAK. You said you are the one who sort of initiated the conversation with Dr. Sunderland and Pfizer, correct?

DR. FRIEDMAN. Yes.

MR. STUPAK. Before you introduced Dr. Sunderland to other Pfizer officials, did you have conversations with him about what his role would be in this research?

DR. FRIEDMAN. Yes. Can I clarify what that conversation was?

MR. STUPAK. At any time did money come up during that time as--

DR. FRIEDMAN. No, never.

MR. STUPAK. --payment for samples or for data?

DR. FRIEDMAN. It was a discussion of a scientific collaboration only.

MR. STUPAK. And do you know how money came up in this whole opportunity or this--

DR. FRIEDMAN. I wasn't part of those discussions.

MR. STUPAK. Who at Pfizer would be?

DR. FRIEDMAN. Kathy Smith would probably be one person. Barry Hess would be another.

MR. STUPAK. Dr. Insel, according to our information, Dr. Sunderland is still on the payroll at NIH?

DR. INSEL. That is correct.

MR. STUPAK. Is any action being taken?

DR. INSEL. His case, as you know, was reviewed by the Office of Management Assessment as part of conflict-of-interest concerns. There was a recommendation made, and the case was referred to the Commissioned Corps of the Public Health Service. He is technically a Commissioned Corps employee.

MR. STUPAK. So the recommendation was made. When was that--to the Corps?

DR. INSEL. I sent that forward I believe on November 21, 2005.

MR. STUPAK. Two thousand five. As far as you know, did anything happen on that recommendation?

DR. INSEL. I have called and sent notes subsequently and as far as I know, there is no decision made yet by the Commissioned Corps.

MR. STUPAK. What was your recommendation?

DR. INSEL. My recommendation, which I believe you have in your package, was, I sent forward the Office of Management Assessment review--essentially it was about a five-page set of findings--and I gave them a one-paragraph cover note saying that I was really disappointed, that I thought of Dr. Sunderland as one of the people who had made tremendous contributions to the agency, but that I had been informed by the Office of Management Assessment that civil service employees who had similar levels of violations would have been recommended for termination.

MR. STUPAK. So were you recommending his termination?

DR. INSEL. I can't actually do that, sir. I don't have the authority.

MR. STUPAK. I am not asking if you terminated him. I am asking if you made a recommendation that he should be terminated.

DR. INSEL. Well, I tried to explain exactly what I said, that I told them that given the severity and the concerns about these findings, that had he been in the civil service, he would have been likely terminated based on what I had been told by the Office of Management Assessment. They will have to make their own determination about that at the Commissioned Corps.

MR. STUPAK. So you don't want to make a recommendation then?

DR. INSEL. In fact, I can't. I can't do any more than refer the case--

MR. STUPAK. How about Dr. Molchan? Would you be her supervisor?

DR. INSEL. I am not Dr. Molchan's supervisor.

MR. STUPAK. If she was to get tenure, would you be involved in the process of whether or not she would receive tenure at NIH?

DR. INSEL. She is currently in the National Institute of Aging, so I wouldn't have anything to do with that. If she were to come back to the National Institute of Mental Health and she were a tenured investigator, I would be involved as in my current temporary role as the Acting Scientific Director for about another month.

MR. STUPAK. So accountability then would depend upon the institute? The National Institute of Mental Health, that would have had the accountability?

DR. INSEL. Let me ask you to unpack that a little bit more in terms of accountability. Accountability for what in this case?

MR. STUPAK. Well, in this case let us say Dr. Sunderland. He is a Corps individual so you don't have any control over that, right?

DR. INSEL. Right.

MR. STUPAK. So who would have accountability over him?

DR. INSEL. Well, this is where it gets complicated. So indeed he is an employee of the Commissioned Corps. He is essentially detailed to the National Institutes of Health where he has been for some 24, 25 years. His supervisor is the Scientific Director of the Institute and so--

MR. STUPAK. Of NIH?

DR. INSEL. Of NIMH in this case, so we are one of 27 components of the NIH, and NIMH has--

MR. STUPAK. Well, let us put it like this. We find it a little funny on this side of the dais that Dr. Sunderland seems to still be working and does not seem to have any problems but the person who came to the committee with her concerns cannot get tenure at NIH, so we have some real questions here on this side so I guess I am trying to figure out who is making these--

DR. INSEL. Let me tease these two things apart. You say you find it a little funny that he is still there and there is--

MR. STUPAK. I find it suspicious.

DR. INSEL. I actually find it a real concern. This has been 2 years since you have given us some information. We have done a very thorough review. We made some recommendations. We made a referral. We are now 7 months down the road and this gentleman is still waiting to find out about his fate. I would separate that from the question about tenure of another scientist. Now, the decision about tenure--

MR. STUPAK. Now, the witness yesterday said that her supervisors were discouraging her from talking to the committee or discouraging her from blowing the whistle, if you will, and then when we find she doesn't receive tenure, I guess that is--we find that suspicious.

DR. INSEL. So if I may, if I can back up.

MR. STUPAK. Sure.

DR. INSEL. She was an employee of the NIMH until I believe 1996, 1997. At that point in time she was not on what we call a tenure track. That is, she was essentially in a training position but an extended one. She did apply for a tenure-track position. It is my understanding that was done in 1997 and that is a competitive process both internal and external. The NIMH, before they would--or NIH, before they would give tenure to an intramural scientist, they are going to do a very though competitive process to make sure we have got the best and the brightest person.

MR. STUPAK. Sure. We find it amazing or amusing that she has 50 co-authored reports with Dr. Sunderland and nothing happens to him but she doesn't get her tenure and she is still waiting, but all those reports for one seem to be beneficial.

MR. WHITFIELD. The gentleman's time has expired.

MR. STUPAK. Thank you.

DR. INSEL. I would be happy to respond to that if I may.

MR. WHITFIELD. Okay.

DR. INSEL. All I can say that in the tenure process, it may seem ironic to you, but in fact, having 50 papers with your supervisor is not a plus. You are looking for someone who is an independent thinker, who has created their own area of research, who can come in and function independently with their own resources, which is what we define as tenure track or tenure. She certainly was considered in that process. He had nothing--he was not on that committee. Obviously this is done by an independent group. They did have a short list. My understanding is that she didn't make the short list and that happens all too often.

MR. WHITFIELD. We will go ahead, and if we have time, we will come back with some more questions. Dr. Burgess, you are recognized for 10 minutes.

MR. BURGESS. Thank you, Mr. Chairman.

Yesterday during our questioning, the issue came up. Dr. Molchan said that this concept of the lithium study was one that she brought to the lab. It was not a project she was assigned after arriving there. But then when the contract or whatever expired and she leaves the lab, is that unusual then for that particular arm of research just to stop and no one to pick it up and continue that? Would that be the standard operating procedure of the NIH in that type of situation?

DR. INSEL. So if I may answer, it is a very in some ways complicated question because it depends on the individual lab and the individual project, but if I can speak to this particular case, I think it is important for the subcommittee to recognize that that was a study that essentially stopped accruing patients early in 1993. She did submit annual progress notes to the Institutional Review Board and the one in 1995 says that she would like to keep the study open even though it has been capped. She hasn't brought anybody else in 2 years because she thinks there may be an opportunity to do additional studies. But in August 8 of 1996, she actually sends a note in the annual note to the board saying that she would like to now terminate the study. She leaves the Institute, as I understand it, in 1997. Now, remember, there has been no additional accrual of patients since 1993 and there have been some papers published in the meantime, but she goes off and leaves for another agency, which is not actually a discovery agency like the NIH, it is a regulatory agency, the FDA, and as she said yesterday, I think my understanding was that this was her project, that wasn't a project of her supervisor's, one that she brought forward, so I don't think in a case like that it would be surprising after the person who had initiated the project decided to terminate it, that no one else decides that they want to pick up on it. That is my understanding of how this took place.

MR. BURGESS. If I understood the tone of questioning correctly yesterday from the committee, there seemed to be a sense that there should be some type of central database for sensitive or delicate tissue samples and that someone at NIH should oversee that. Now, I tried to get a sense from Dr. Molchan as to how many blood, urine, tissue samples there might be housed in the various refrigerators and warehouses at the NIH just in the intramural part here in Bethesda, and I really no one would even hazard a guess at a number, but I would suspect those numbers of samples must be in the millions to tens of millions when you think of all of the test-tube racks and all the refrigerators and all the freezers contained in all those buildings out

there. Mr. Chairman, I might point out, all those buildings are named for appropriators, not authorizers, as we reconsider the reauthorization of the NIH.

But is there currently any type of central way that you keep track of this? If someone were to go out there today and start a spinal fluid study on Alzheimer's patients, would those samples be logged in, coded, and someone keep track of that over time?

DR. INSEL. So the investigator, and by that we could be talking about a lab chief or a staff scientist who is involved, would have a tremendous investment in the samples they are collecting, and we would expect them as part of their stewardship to do a very careful documentation of what they have and where they have it and how they are managing it. But the question you are asking, is there a central database, that is, of 54 scientists. Do they at some point pool all of their data on all of their freezers and refrigerators and what they have at any given time? The answer is no.

MR. BURGESS. And is it a reasonable expectation that this committee might have that that would ever be in place or is the problem just that the number of samples is just too large?

DR. INSEL. I think it is a really interesting question to consider, and I think part of what happens, and as the Chairman said, we are sort of looking at some of these policies through the prism of a single case. We want to make sure that whatever solutions we come up with don't create problems of their own, and what you don't want is a bureaucracy that makes it impossible to move quickly and to make discoveries in an environment like the NIH. At the same time you want to make sure you can manage what you have. As we often say, if you can't measure it, you can't manage it, so you have to know what is there and you have to be able to know what has been used and what still remains.

Up until this point, we have left it to the scientists themselves to make those determinations and then we review the scientists based on their stewardship. The question you are asking is, should we put something in place in the era where we have these large lab management software systems? Do we need that? Well, some of the institutes have been doing that and already they are putting those ideas out on the table and trying them out. Some of them have already taken them out on the road a bit to see how they work. Dr. Gottesman may tell you a little bit more about that. It is not as simple as it sounds. It is not necessarily the solution to all problems but I think at this point is one thing that we really want to look at very seriously, and we are in the process right now already in the last few weeks of pulling together inventory of everything we have got, making sure we know what has been used and what hasn't and trying to figure out what would be the impediments to actually

coming up with the kind of central database that actually might also articulate with other kinds of clinical research data that we have. So I think there is an opportunity here, and we actually owe it to the subcommittee--

MR. BURGESS. I don't want to interrupt you but my time is going to draw short. There are a couple things--I do want to explore this line of questioning a little further. Not commenting on the rightness or wrongness of what Dr. Sunderland did, would we even be having this discussion if those samples had been used and there had been a blockbuster breakthrough? I mean, myself as a taxpayer and a consumer of medical research at the other end, I might see that as a good thing and a worthwhile thing. Would we even be having this hearing if there had been a wonderful extrapolation of that data and we had seen the onset of Alzheimer's delayed by ten years per patient?

DR. INSEL. Well, I appreciate that question. I do think that it is important to separate out scientific collaboration, which was an exciting and promising and I think very useful endeavor, from this question of conflict of interest. I think before you came in, I said the true north here has to be the question of separating out public role, official duty, from private gain, and if that wasn't on the table, then we are here to congratulate Dr. Sunderland on having done I think a really excited scientific collaboration which as you heard from Dr. Friedman may actually bear some really important discoveries for families with Alzheimer's disease. So the question of having actually worked with industry to come up with new biomarkers for Alzheimer's, I think everybody would cheer him on to do that.

MR. BURGESS. Would it have been a tragedy if that breakthrough could have occurred and it didn't occur because those samples sat in a freezer somewhere--

DR. INSEL. Absolutely.

MR. BURGESS. --for 15 years?

DR. INSEL. I think it would be a real mistake to decide based on our considerations of these issues that when you have residual samples from a study like this that has been closed that we just dispose of them because they may have true value and could be used for discoveries. We have examples over and over again--hepatitis B, hepatitis C, AIDS where it is stored samples that have really brought out fantastic discoveries for human health. There is an opportunity to do that here and it still may happen.

MR. BURGESS. Let me ask you this, because it kept coming up yesterday. Is the scientist, the principal investigator under any obligation to go back to the person that sample is collected from and to reissue or redirect permission to study--

DR. INSEL. Reconsent?

MR. BURGESS. Reconsent. Yes, sir. Thank you.

DR. INSEL. The obligation is not to reconsent but to be very clear is that if you have got samples that are stored for a study that has been terminated, we call those residual samples and you have got them in the freezer and you want to use them again for any purpose that involves research, it is not up to the scientist to decide whether that should go forward or not. We have a very clear new policy in place that says as of just the last few days that we want people to go back to the Institutional Review Board to let them know what new use they would like to make of remaining samples because we don't want to leave that in the hands of the scientist.

MR. BURGESS. What would the policy have been when the original lithium study was closed in 1996 or 1997?

DR. INSEL. I think the policy there was just very general, and if someone--I could certainly understand how someone could say well, these samples were taken to study neurochemistry in the cerebrospinal fluid, we are studying neurochemistry in the cerebrospinal fluid for Alzheimer's disease and could decide they might be used at that point in time. Remember, now, that would require additional review.

MR. BURGESS. But your new policy that is in place would not leave one person as being the final arbiter as to what to do with these potentially very valuable samples; there would be oversight by the Institutional Review Board. Is that correct?

DR. INSEL. Precisely.

MR. BURGESS. Thank you, Mr. Chairman.

MR. WHITFIELD. Thank you, Dr. Burgess. At this time I recognize Ms. DeGette for 10 minutes.

MS. DEGETTE. Thank you, Mr. Chairman. Dr. Insel, Mr. Burgess raised some thoughts in my mind about exactly what the IRB process is for these residual tissue samples, and you told him that it would be a shame if the result of this issue was that these samples were just destroyed, and I agree with you, but I also think, and you might know, I have introduced legislation about patient protections and all this, and you said we didn't need a reconsent process. Now, as I understand it, in this situation the original tissue donors did give a consent process and it went through IRB review, right?

DR. INSEL. That is correct.

MS. DEGETTE. But I am not suggesting a reconsent process, which I think would be impracticable, but I do think in the original consent process, you need to have some kind of informed consent for the donor that these tissue samples may be used later on for some kind of a different experiment or process, correct?

DR. INSEL. Absolutely. You will hear later from Dr. Gottesman that we actually have a new policy that will come into place that has to do with having to define what is the disposition of either stored samples or samples following the termination of the protocol.

MS. DEGETTE. Right, and this has been a problem not just with the NIH but with other research institutions recently, correct?

DR. INSEL. That is right.

MS. DEGETTE. And then you said that you would--that for a subsequent study on these tissue samples that might be a different study, they would have to go back to the IRB, right?

DR. INSEL. So I should just clarify because I knew we were short on time. There are two options. In some cases--I should say three options. In a case like this where you are studying Alzheimer's disease, I don't know this but it very well may be that, for instance, the subjects in this lithium protocol were all dead by the time that the scientists wanted to use the samples.

MS. DEGETTE. Right.

DR. INSEL. That puts them into a very different class.

MS. DEGETTE. I know, but for a subsequent study. I am not talking about the consent anymore. I am talking about going back to have the subsequent study approved by an IRB. That is what you--

DR. INSEL. Right. It would either need to go--well, it would go to the IRB to ask the question, does this require reconsenting, does this require review, should this even be done, and there may be--

MS. DEGETTE. Just for the threshold issues, would that be a full IRB process or would that be like a threshold IRB process?

DR. INSEL. Right. These were questions that we are now entertaining. I might ask Dr. Rosenstein, who is really the expert on the IRB issue, to comment on this because this is exactly the discussion we have been having in the last few weeks.

DR. ROSENSTEIN. You are asking about IRB approval of new use of existing samples?

MR. WHITFIELD. Excuse me, Dr. Rosenstein. You are going to be testifying, so if you just stand up and raise your right hand.

[Witness sworn]

MS. DEGETTE. Right. Dr. Insel said in his statement to Mr. Burgess that for a new study using these leftover tissue samples that there would have to be some IRB process. I don't have a lot of time and I have other questions for him, so if you can answer very quickly, I would appreciate it.

DR. ROSENSTEIN. The Federal regulations require that research with human samples undergoing initial and ongoing review by an IRB. The question has to do with what the ongoing review is for existing samples.

That is the policy that has been clarified. Those regulations have been in place a long time but haven't always been followed as completely as they should be.

MS. DEGETTE. And in fact, it wasn't followed in this case, right?

DR. ROSENSTEIN. Correct.

MS. DEGETTE. Okay. Dr. Insel, let me get back to a couple of other things. Now, I think you testified earlier that you became the director of the National Institute of Mental Health in 2002, correct?

DR. INSEL. Yes.

MS. DEGETTE. And Dr. Sunderland at that time was a lab chief there, right?

DR. INSEL. Yes.

MS. DEGETTE. And so you were there in 2004 when we had our hearings in this subcommittee and we found out that there were what we thought then was around $500,000. Now we now it is over $612,000 in unreported payments to Dr. Sunderland, correct?

DR. INSEL. I haven't seen all the numbers but I will accept those.

MS. DEGETTE. It was lots of money. Can I assume that you know what the payments were for or did you ask him what they were for?

DR. INSEL. Well, I have spoken with him about this but I have to clarify that. I had not seen the documentation of any consulting agreements until very, very recently, only in the last few days, so I couldn't tell you what those payments were for at that--

MS. DEGETTE. Why didn't you see the--I mean, if this has been going on for 2 years?

DR. INSEL. Right. So, this came out originally in June of 2004 that this subcommittee brought this issue to the NIH and of course all of us began to move into high gear to try to understand what was going on here with some of our scientists. The NIH decided that there should be only one investigation NIH-wide and that investigation would be done by the Office of Management Assessment. We were told specifically not to pursue any of these questions with our own scientists, go back to work, make discoveries, continue to have an impact on human health--

MS. DEGETTE. So you assumed that they were investigated?

DR. INSEL. Precisely.

MS. DEGETTE. And now why--

DR. INSEL. Well, not only did I assume, I was--this was something that we all agreed would be done by one body.

MS. DEGETTE. Right, based on what you were told. I am not being critical. And so when you read those consulting agreements that he had or whatever they were 2 days ago, that was in preparation for this hearing today?

DR. INSEL. Right.

MS. DEGETTE. Okay. Now, you had testified earlier to Mr. Stupak's question that you went through the whole process of how someone like Dr. Sunderland gets removed and so on and you told Mr. Stupak that you have concerns that it has taken so long to figure out a disposition of his situation. Would that be an accurate statement?

DR. INSEL. I have concerns.

MS. DEGETTE. What concerns are they?

DR. INSEL. Well, it just seems to me that in this case, it has taken 2 years before there is any penalty or any decision made about someone's career. I think that is an awful long time.

MS. DEGETTE. Especially in light of these egregious examples here, right?

DR. INSEL. Even if we didn't have egregious examples, I really think that in the spirit of due process, we deserve and our scientists deserve resolution of some of these issues so that we can all move on. We need to heal as--

MS. DEGETTE. Have you let your superiors know that, that they need to get some kind of a resolution of this case?

DR. INSEL. I have spoken to several people and--but you have to remember, this case is no longer in the National Institutes of Health. It is now sitting elsewhere.

MS. DEGETTE. I understand. Now, I want to ask you one more question. You were talking earlier about these computer programs that we have and ways that we can get central registries of these tissue samples and so on, and you were talking about--it sounds like your institute and the other institutes are at the very early stages of talking about how we catalog and cross-reference this data. Would that be accurate?

DR. INSEL. So we are at the early stages of talking about it in a systemic way. Individual large labs already do a lot of bar coding, a lot of lab management systems. This is being done. And as you heard yesterday from Dr. Molchan, Dr. Sunderland has an extremely good data-tracking system. That is not the problem here. So there are individual labs who are doing this very, very well. The question is, should we be doing it as an institution, as an agency. Should we have all that rolled into one interoperable database.

MS. DEGETTE. Well, I have had many, many short and long conversations with Dr. Zerhouni, and as you know, with the NIH reauthorization, his concept is more centralization of funding and more cross-institute collaboration on research which I happen to agree with that vision, but it seems to me if we don't even have the basic mechanism in place for cataloging and cross-agency utilization of tissue samples, it would be very difficult to have that kind of collaboration

without the risk of many situations like the Sunderland situation coming up. Wouldn't you agree?

DR. INSEL. I agree with what you are saying but again I want to clarify. I think you have to separate out issues of data tracking, which in some ways are software systems issues that we can do, anyone can do. That is different than the issue of oversight and how you make sure that people are doing the right thing, and that still--

MS. DEGETTE. Right. It doesn't sound like we have got either one in place though.

DR. INSEL. Well, what I am telling you is that we are looking at ways of getting the tracking in place but if we simply did that, we wouldn't fix the oversight issue. The oversight issue is the one that really needs to be a focus right now. How do we make sure that people are doing what they are supposed to do. We come back--I think you weren't in the room yet but--to true north, the central principle, public office separated from private gain.

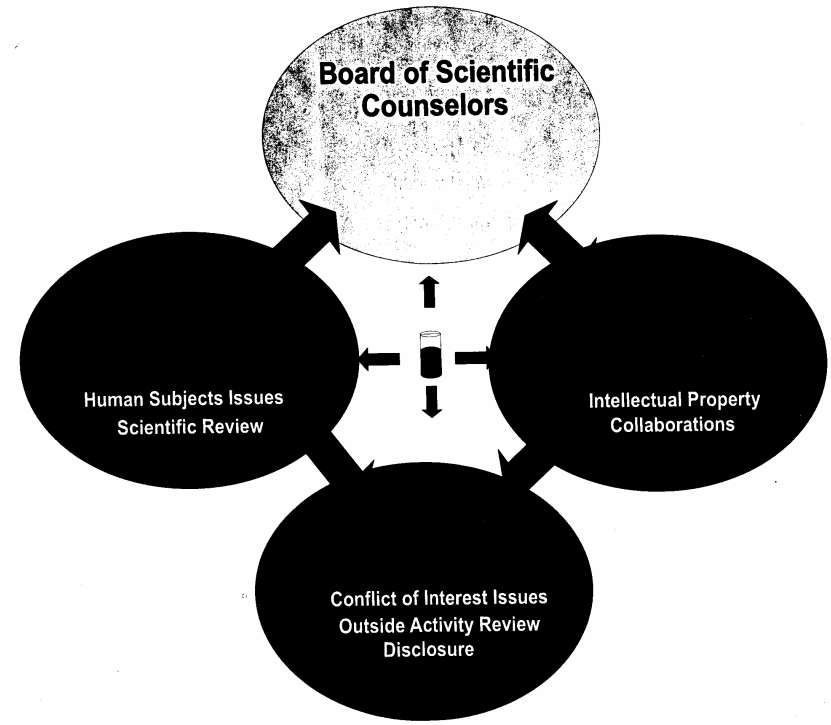
MS. DEGETTE. Right. Well, I am with you there. What more do you think we can do to make that oversight a reality because the last set of hearings we had, and I was there, I was on this subcommittee, it was 2 years ago and yet here we are again.

DR. INSEL. So Mr. Chairman, if I may, we have actually brought a little diagram to give you some ideas of how we think about doing this, and these have been handed out to you.

MS. DEGETTE. Mr. Chairman, I would ask unanimous consent that the copies be made a part of the record.

MR. WHITFIELD. Without objection. The copies are being passed out now.

[The information follows:]



DR. INSEL. I wouldn't want the subcommittee to think for a moment that we don't have anything in place for oversight. We have a great number of ways in which this is done, and what this diagram which you will have copies of demonstrates is that there are actually four different forms of oversight for anybody who wants to begin analyzing a clinical sample. There is the Institutional Review Board that looks at the issues of human subjects' protections. There is a Board of Scientific Counselors that looks at scientific quality and whether these are studies that should be done anyway. There is the Office of Technology Transfer that deals with questions around collaborations. And then the deputy ethics counselor, which has a very important role for making sure that there is no conflict of interest. Now, we had all of these in place in 2004 but what we didn't have then were the arrows. I think if there is a vulnerability in the agency, it was that we weren't well integrated, in some ways in the way you are talking about, Ms. DeGette, around trying to have a single agency approach to many of these issues and what we are building in place now both with electronic systems and with human power as well is making sure that there is cross talk across all of these different elements of oversight so that whenever someone applies for an MTA, there would be an opportunity to know whether it is indeed an

outside agency with the same agent and to make sure that this goes to the Institutional Review Board at the same time.

MR. WHITFIELD. The lady's time has expired. At this time I recognize Mrs. Blackburn of Tennessee.

MRS. BLACKBURN. Thank you, Mr. Chairman. I thank each of you, and I am going to stay right there on the same issue where Ms. DeGette was, so basically what we have got are three primary groups that are doing research. We have the NIH, we have academia, and we have private industry, and what we are trying to figure out is how we have appropriate oversight and not impede science. What I feel like I am hearing from you is well, we have turned a blind eye to what the interface would be between those groups and we have kind of swept those relationships under the rug, and let relationships occur, let payments occur and then until it became an awareness issue, we chose not to address it. Because what I am hearing from you now is well, we didn't have a way to inventory samples but now we are looking at the fact that we need a comprehensive inventory. We have a brand-new policy of going back to the review board and then in February 2005, Dr. Zerhouni established a policy on outside consulting. So Dr. Insel, what I think I am hearing from you is, you didn't think you needed the oversight until it came to the attention that there was misbehavior and wrongdoing and I understand and appreciate your concern for saying that someone deserves the due process through the situation and consideration but our taxpayers hold us responsible for exercising the oversight in being certain that their tax dollars and the research dollars are being spent appropriately and properly. So to go back, we have gone a long way around the horn with Ms. DeGette's question and my question, so, very quickly, how do we have proper oversight and not impede the scientific research?

DR. INSEL. Well, I like the way you put your question because that really is finding the sweet spot between making sure that we have the oversight we need but at the same time not putting in too many speed bumps that delay our ability to find a discovery for Alzheimer's disease or autism or another very serious illness, and that is a delicate balance in some cases. Some of the things that--

MRS. BLACKBURN. The action item. You know, let us not talk it to death. What do you see as the bullet points, the action items?

DR. INSEL. So for us the action items are new policies, and let me just go through what we have done even in the last few weeks. You know about Dr. Zerhouni's change last year. We put a moratorium on the use of stored samples until we can develop a policy that makes sure that every stored--

MRS. BLACKBURN. Are you slowing down any research by putting that moratorium into play?

DR. INSEL. We very well may be. We don't know that yet. We won't know that until we have a full listing of what is there.

MRS. BLACKBURN. Okay.

DR. INSEL. We are requiring that all collaborations be documented with a written agreement so that we have an opportunity to find out what is being done, where it is being done, and who is responsible, and those things can be reviewed both by, as I showed you with this diagram, by four different groups. And in addition to that, we are making sure that the people within the intramural program, the scientists are fully educated about what it is these new expectations entail. We have had two faculty meetings in the last month to go over these issues. Dr. Gottesman will talk more about some of the things that are being done NIH-wide.

MRS. BLACKBURN. So these are all your band-aids? You basically have four band-aids that you are putting in place until you establish a policy?

DR. INSEL. Well, we have a policy but it is not necessarily a true fix.

MRS. BLACKBURN. And for how many years has the NIH being doing research?

DR. INSEL. Clinical research for close to 60 years.

MRS. BLACKBURN. For 60 years, so basically you have flown 60 years without a policy?

DR. INSEL. We have a number of policies, but you have to recognize that science changes, the needs change--

MRS. BLACKBURN. I recognize that, and I appreciate that, and I have great respect for the work that you do and I want to see that work continue. In that vein, how many employees does the NIH have in total?

DR. INSEL. I think the full number is about 17,000 to 18,000 for all of NIH.

MRS. BLACKBURN. Seventeen to 18,000, and how many of those are researchers?

DR. INSEL. It depends on how you define a researcher. I can tell you--

MRS. BLACKBURN. How many are working in the area of research?

DR. INSEL. Well, I would assume that almost all of them are involved in some form or another with the mission of the agency, which is research. I can tell you more from my own institute, NIMH, where we have 700 employees. We have 55 or 54 tenured or tenure-track scientists and we have got another 60 who are staff scientist or staff clinician positions, and there are about another 150 to 200 post-doctoral fellows and other kinds of trainees.

MRS. BLACKBURN. Okay. And then your total budget is how much?

DR. INSEL. Our budget for the entire institute, NIMH, is roughly $1.4 billion, and about 10 percent of that goes to the intramural program, which is the subject of this hearing, which is about $159 million in the current fiscal year.

MRS. BLACKBURN. Okay. Out of that total budget of $1.4 billion for NIMH, what percent goes to research?

DR. INSEL. There is about 94 percent, I believe, that goes to research support and there is another six percent that is used--I think that would be right--for research management, which is providing the administrative infrastructure for the research enterprise.

MRS. BLACKBURN. All right. Great. Now, in your role as the director at NIH and NIMH, have you ever performed any outside consulting duties?

DR. INSEL. No.

MRS. BLACKBURN. You have not? Have any of you at the table performed outside consulting duties in your roles? You have never had outside consulting agreements? Dr. Friedman, have you? No? Okay. All right. Going back to Dr. Molchan from yesterday, I found it so interesting that she could have put so much work and energy into a project and then it comes to a stop, so let us look at these researchers and the research projects that you do. You used the term "independent thinkers" in talking about your researchers. How do you prioritize your projects? Do you let the researchers choose what they want to work on? Do you have an agency agenda? Do you all sit down and say we need to work on this, that or the other? So how do you mesh those or are they just flying interconnectedly and just recently brought together?

DR. INSEL. So again, we are focusing on our intramural program, this small group, this jewel in the crown that is here in Bethesda which is about 10 percent of what our institute is about. In that case, we have a relatively small group of senior scientists who we look to help generate the most exciting innovative science, high-impact science that they can, and they are reviewed every 4 years, and that review is a very rigorous one in which we bring in a panel from outside the agency to look at three things: how the research is going, is it going in the right directions, are they doing the most cutting-edge work, are they innovative; stewardship, how well is this person actually using the resources that have been given and mentorship, how well are they training the next generation.

MRS. BLACKBURN. And how long has that review process been in place?

DR. INSEL. Oh, it has been going on at least as long as I know about the agency, which is over 20 years.

MRS. BLACKBURN. Okay. Great. And then how often do these researchers choose a project and then choose to terminate a project? Does that happen very often, and do you have a library of research that other researchers can go back to if they are working on some type of research and then they find that there are applications for something that was not intended and they think, well, this may work. What is your library process?

DR. INSEL. To answer your first question about how often does someone hit a dry hole, it is often, and that is to be expected. The intramural program is for high-risk, high-yield science. High risk also means that it may often fail, and we actually don't see that as a problem. In terms of having a library of negative results, that library is in publications. That is generally the repository of information for our field and people look to publications both for discoveries and for discoveries that can't be replicated.

MRS. BLACKBURN. Very good. All right. I think that is about it, and I have only a couple seconds left so I yield it back.

MR. WHITFIELD. Thank you. At this time I recognize Mr. Inslee.

MR. INSLEE. Thank you. Dr. Insel, I was looking at this quite colorful chart and it sort of circles a little vial here in the middle and I guess that vial is probably where they put the answers and it only looks half full on this chart, and it sort of I think is a pretty symbolic representation. It just seems to me there is some ambiguity in these processes that needs to be fixed. That is an observation of somebody just new to this issue. But I want to ask you specifically about the situation with Dr. Sunderland. I read in the papers that Mr. Robert Muse, Dr. Sunderland's attorney, said his client "didn't receive a dime for providing anything to Pfizer. He received fees for consulting as for lectures. These are known to NIH and they were permitted under NIH rules." And I guess the question I have is, in the relevant time period, do you have reason to believe that NIH had information regarding the specific financial relationship regarding the collaboration and involving the use of human tissue samples that were originally with NIH?

DR. INSEL. If you could clarify when you say the relevant time period.

MR. INSLEE. Well, before 2 days ago. How is that?

DR. INSEL. I believe some of this information came to the investigation that was done starting in 2004 by the Office of Management Assessment.

MR. INSLEE. So before an investigation started, did NIH have information about the specifics of the collaboration that involved apparently use of NIH tissue samples?

DR. INSEL. Absolutely. We had an MTA, a materials transfer agreement, between Dr. Sunderland and Pfizer that documented that there was a collaboration to send over 250 cerebrospinal fluid samples for analysis of proteins potentially relevant to Alzheimer's disease.

MR. INSLEE. So NIH was aware that there was a financial remuneration going to be paid to Dr. Sunderland?

DR. INSEL. Absolutely not. So again, let me clarify. We have to separate here a scientific collaboration which we encourage and which we actually want to promote as long as it is done as one's official duty from an outside activity consulting arrangement with the same agency, which has never been permitted, and in this case was undisclosed.

MR. INSLEE. So I want to make sure I understand. The financial remuneration was undisclosed but the transfer of the tissue samples was disclosed?

DR. INSEL. Exactly. And bottom line, had he come to you or anyone else at NIH and said at that time my arrangement is that I will be receiving financial remuneration for collaborative services, I will be using NIH tissue samples, they will be removed from NIH physical custody, is that permissible under our rules, what would have happened?

DR. INSEL. There is a way to do this and it is something that is called a cooperative research and development agreement. So someone could say--a scientist could say I would like to transfer blood samples to company X and I want company X to pay my laboratory to support a junior investigator. That is actually perfectly permissible and it is also a way of dealing with intellectual property. All of that has been worked out so there are ways to do this but that is not what we are talking about here.

MR. INSLEE. Well, in what way is it different? I guess what I am saying is, had permission been sought by this particular investigator for this relationship, would it have been granted?

DR. INSEL. Not in the way that it has been described in the staff report. That kind of outside activity, consulting, would not have been permitted for someone who had a collaborative arrangement with the same agency. What I am telling is that if someone wants to collaborate, we try to encourage that. If there is intellectual property at stake, there is actually a way to manage that. That is called this cooperative research and development agreement. That was not actually in the case in this particular example.

MR. INSLEE. This may clear to everyone listening to this but I want to make sure I understand it as well. In what way would it have not been consistent with those rules? That it was going to outside the NIH financial structure or was it going to the person who took possession? In what way would it violate those rules?

DR. INSEL. Because what this does is, it violates the fundamental principle, which we keep coming back to. It is that overlap between public office and private gain, and the way that we would manage that generally is with this CRADA mechanism and allow someone to actually pursue a collaboration and potentially also seek intellectual property protection or patents. The mechanism used here, the materials transfer agreement, doesn't actually permit that and it is not reviewed in the same way. There is a very extensive review process for a CRADA that ensures that there is no outside activity, that there is no private gain involved. That was not the case. This particular case was not reviewed in that way.

MR. INSLEE. What is the sanction if there is a violation of any of the several policies that you have talked about?

DR. INSEL. What is the penalty?

MR. INSLEE. Yes.

DR. INSEL. It is really wide range and it depends on the severity of the penalty and it depends on whether--for instance, in a case, and I don't want to go into this particular case because this is already under investigation elsewhere--but one could imagine that the central question that would be asked is, had someone sought approval, would it have been granted, is there actually an inherent conflict of interest here, those kinds of issues, and so the sanction, the penalty would range from reprimand to suspension to termination, depending on how those particular factors line up.

MR. INSLEE. Thank you.

MR. WHITFIELD. At this time I will recognize the full committee Chairman, Mr. Barton.

CHAIRMAN BARTON. Thank you, Chairman Whitfield and Mr. Stupak, for continuing this hearing from yesterday.

My first question, Dr. Insel, what are the inventory control practices now in place at NIH for human tissue sample collection, maintenance and tracking purposes?

DR. INSEL. As I said before you came in, Mr. Chairman, we have no central tracking of human tissue samples NIH-wide at this point.

CHAIRMAN BARTON. Is there an effort to initiate such a central tracking system?

DR. INSEL. There certainly is. There has been a lot of discussion partly as the result of the work of this subcommittee to figure out how we can do this much better, and I can give you a quick rundown of some of the things that we are involved with if that would be helpful.

CHAIRMAN BARTON. Now, we are preparing an NIH reauthorization bill which I hope to have public within the next month if not sooner. Is this something that should be a part of that bill?

DR. INSEL. I think we need to dig it into a bit. When you think about how you want to specify--I guess it is a question, if you will, of granularity. Do you want to have a tracking system that goes after every freezer, every shelf, every sample and every component of every sample? I think there has got to be a point at which we think about what the details would mean, and as we said earlier in the hearing, finding this sweet spot between promoting discovery and rapid advances in science but not putting in too many speed bumps for the purpose of oversight. We need it, but we need to find a way to do it so that we are still able to make the kind of progress we need.

CHAIRMAN BARTON. Well, the staff memo that is attached for this hearing says the current NIH system for human tissue sample collection and maintenance is fairly loose and ad hoc. Is that an accurate assessment?

DR. INSEL. I think if you take the pejorative term, pejorative connotation of ad hoc out, I would say that it is ad hoc in the sense that it is delegated to individual scientists who have the greatest investment in their own samples. They have collected them, their careers depend upon them, and I believe as you heard yesterday from Dr. Molchan, even in this case, which has generated so much interest in tissue tracking, you have a scientist who apparently had a pretty good handle on exactly where every sample was and how to find it and he was able to generate 13 years after the fact the samples in question so I am not sure that I would say that it is loose, but I would say that it has been delegated to individual scientists to make sure that they are doing the job the way--

CHAIRMAN BARTON. But you are in agreement that the current system can be improved upon?

DR. INSEL. I think the current system needs to be improved upon. The question is how. We want to make sure that our solution doesn't create new problems, and that is why I don't want to rush into this.

CHAIRMAN BARTON. All right. Well, let us go on to the next subject. We have one of your researchers, a Dr. Trey Sunderland. Is he still on staff at NIH?

DR. INSEL. He is.

CHAIRMAN BARTON. Is he on full capability or is he on leave with pay or what is his current status?

DR. INSEL. He comes to work. He is getting, as far as I know, full salary and he stills serves as the chief of the geriatric psychiatry branch.

CHAIRMAN BARTON. Okay. So he is still on active duty without any--

DR. INSEL. That is correct.

CHAIRMAN BARTON. Are you aware that the subcommittee has got documents in evidence that leads us to believe that he has been

compensated--I don't know how to put this--in a fashion that doesn't appear to comport with the regulations in place at NIH?

DR. INSEL. I have seen the subcommittee documents that suggest that he received outside income for consulting with Pfizer.

CHAIRMAN BARTON. Well, we have some evidence that shows $285,000 in payments that appear to be inappropriate, another $200,000 in various expenses that appear to be inappropriate, and over $300,000 in lecture fees that may or may not be appropriate. Now, those numbers add up to three-quarters of a million dollars. What is the average salary of somebody in his position or similar position at NIH right now?

DR. INSEL. Well, for someone who is a lab chief, the salaries vary between--generally between $150,000 and $200,000.

CHAIRMAN BARTON. So three-quarters of a million dollars in compensation of a questionable nature should raise some eyebrows. It would certainly raise eyebrows if a member of this committee--I think our average salary--it is $165,000. If I had outside income of $750,000 that I didn't report on my financial disclosure statement and came from people who had pending legislation before this committee, I would have an ethics investigation by the Minority party and probably a contested primary and every newspaper in the country asking for my resignation from Congress.

Now, I understand that Dr. Zerhouni has changed the ethics requirement at NIH and some of what happened with Dr. Sunderland predated that, so it could well be possible that some of the things that are now unacceptable under the regulations at NIH were acceptable. I haven't seen a timeline so I am not going to say with certainty that all of this compensation that I just enumerated will turn out to be unacceptable, but I will say with certainty that it seems puzzling to me that he still is in his current position with no apparent reaction from the administration at NIH.

DR. INSEL. Well, Mr. Chairman, if I may, I think it is important to realize that there has been an extensive investigation. There has been a set of findings. The case has been referred. He is an employee of the Commissioned Corps. The NIH itself doesn't have the authority to either hire or fire Dr. Sunderland. This is done through the Commissioned Corps.

CHAIRMAN BARTON. But do you have the authority to put him on leave with pay? You do have the authority to transfer him.

DR. INSEL. In fact, my understanding is that his disposition of his--of where he works and what he does is at this point in the hands of the Commissioned Corps, and if I can add--

CHAIRMAN BARTON. What would happen if Dr. Sunderland went out and robbed a bank and then reported to work? Would he report to work with full benefits?

DR. INSEL. Let me explain that. Had he been a civil servant and that is the case for over 90 percent of the scientists at NIH, this would have been resolved months ago and we wouldn't be having this discussion at this point in time. We made a recommendation November 21. We made the referral at that point to the Commissioned Corps. It is really out of our hands at this point unfortunately, and I also want to add that I think that fixing this is not enough. I think you need--the subcommittee needs to understand that the NIH intramural program, it is not good enough to just be clean. It has to be Camelot. It has to be the place where no one will have any question about conflicts of interest. There has to be some place in the United States where the public knows that there is no taint, that there is no question, that there is no outside investment that is involved, that this is being done for the public good. This is the place. And for anything to come up that would in any way soil that reputation, we need to take care of it and we need to do more than fix it. We need to actually become the model for how this research is done.

CHAIRMAN BARTON. On a bipartisan basis, subcommittee staff has been working on this for at least 6 months and maybe longer, and the report that I get is that Dr. Sunderland failed to provide information, failed to cooperate. What little information that we have gotten, some of it appears to be misleading or intentionally inaccurate, and unless I am briefed by you or your staff later today, Dr. Zerhouni's staff, nobody is disputing, that I am aware of, that some of the payments that I just enumerated are not facts, that we misinterpreted, that there is a misunderstanding.

DR. INSEL. So in the--

CHAIRMAN BARTON. And so we have a person who has on the surface suffered no repercussion, none, and you talk about a Camelot.

DR. INSEL. You can see why I am frustrated. I should add that in the past few days I understand that his case has been referred to the Inspector General and to the Department of Justice, that that is based not on what the original investigation focused on, which was the questions about whether there was overlap between official duty and outside activities, that is based on some of the new accusations that the subcommittee has brought to our attention.

CHAIRMAN BARTON. Well, my time is expired. We want NIH to be the crown jewel. I would much rather be here hosting a hearing where we highlight the breakthroughs on Alzheimer's research. My mother has Alzheimer's. I would love to be commending Dr. Sunderland and yourself and the other doctors for medical research breakthroughs that

make life better and easier. It is no fun to be holding this kind of a hearing.

DR. INSEL. Amen.

CHAIRMAN BARTON. But it is inexcusable that in spite of the public changes that have been made at NIH, there really does not appear to be a cultural change where the institution and the members of the institution condemn the kind of behavior that apparently Dr. Sunderland has exhibited. It is really, really disappointing. And with that, Mr. Chairman, I yield back

MR. WHITFIELD. Mr. Bass.

MR. BASS. Thank you, Mr. Chairman, and I am not going to use my whole time here and I follow on with what the Chairman has said. This is a little bit reminiscent of the controversy that we had back at the 1990s at Los Alamos when I was on the Intelligence Committee. It was an issue fundamentally of culture and the relationship that the scientific community had with the administrative community. Obviously the issues there were entirely unrelated to what we are talking about here today. I believe that you have addressed the issue of what Dr. Sunderland's status is. Are you aware of the fact that he may not actually be--there is a possibility that he may not be at his desk all the time, that he has another job somewhere else or he may have a laboratory that he goes to somewhere else? Is that--are you aware of that or not?

DR. INSEL. I am not aware that he has any other employment.

MR. BASS. All told, you have here allegations at least that there is an impropriety involving outside activity and consulting with the same agent. There are issues of activity that is not allowed. There are disclosure issues. There may be patent issues involved. Do you have specific recommendations for NIH or NIMH with respect to what new policies should be enacted over and above what has been done now that would correct this problem and return this agency to what the Chairman or you referred to rather as the Camelot of research entities?

DR. INSEL. Well, I do have a number of ideas about that, and of course, Dr. Zerhouni has spoken to the subcommittee on several occasions to explain many of the things that are being done in the ethics arena starting with first the prohibition against outside activities with either drug companies or pharmaceutical companies, putting in a whole new set of safeguards to make sure that we review any outside activity request, and also having increased requirements for disclosure. All of that was done over the last 18 months. Here we are talking about some slightly different issues which have to do not much or not only with ethical violations but with questions about how our tissue samples and how our clinical samples in general are managed and there I think is part of why I put together this chart for you. I wanted you to see that we do

have several independent programs that oversee how clinical samples are used. I think the challenge for us going forward is providing the appropriate integration of those programs and also the appropriate oversight within each one to make sure that people are doing exactly what they have been approved to do.

MR. BASS. And it is possible that this collaboration and consulting may have actually been of significant benefit to the research effort. Is that correct or not? Is it possible? I mean, did the work that Pfizer did save NIMH a significant amount of time and money or not?

DR. INSEL. I think that is in fact the case. My understanding is that the collaboration was fundamentally to measure two proteins in spinal fluid. The antibody for one of those proteins was a licensed agent that wasn't widely available. It is quite expensive to have those tests done, and Pfizer, as I understand it, agreed to do those free of charge at a tremendous savings to the agency.

MR. BASS. Fair enough. I don't have any further questions, Mr. Chairman.

MR. WHITFIELD. Mr. Stearns.

MR. STEARNS. Thank you, Mr. Chairman. Dr. Insel, you have been at your present position since 2002?

DR. INSEL. November 2002.

MR. STEARNS. You had mentioned in your conversation with members that you can't manage unless you can measure it, and you went on to say that Dr. Sunderland had a great tracking system. I think those were your words just 20 minutes ago.

DR. INSEL. That is right.

MR. STEARNS. In this graph, the committee, trying to identify the collected spinal fluids, found that what Dr. Sunderland provided in 2005 is yellow. Molchan provided 97. This is sort of bluish amber. And this is the accounted for samples. Did you know that all these samples are unaccounted for?

DR. INSEL. Can I ask what you mean by unaccounted for?

MR. STEARNS. Spinal fluid for lithium studies. Do you want me to show you this graph?

DR. INSEL. I haven't actually seen the graph but the spinal--so if we are talking about the study done from 1991 to 1993, we had--there were 25 subjects who were entered into the study. There were 15 who had two lumbar punctures who could have been used for Dr. Molchan's--

MR. STEARNS. Well, the staff is saying this is unaccounted for if you go to that graph. Were you aware that these are unaccounted-for samples that we have no measurement of?

DR. INSEL. I really--with all due respect, I think--

MR. STEARNS. Do you dispute what the staff's graph is?

DR. INSEL. What I would dispute is what is meant by unaccounted. Dr. Sunderland has not, as far as I know, given away all of his spinal fluid to anyone. There are five -70 freezers--

MR. STEARNS. Let me just finish here. I've got a memo here--June 20, 2005, to you--oh, this is your original message and "Gottesman's office has been collecting rules, regulations, and policies. We need the following specific information on GPB protocol: a list of samples that went to Pfizer and not a list of names but a list that shows number of samples and protocol so we can link consents to samples, copies of consents." It indicated that, you were sort of aware of all these unaccounted-for samples. In fact, you were asking for it in this memo. Do you want me to show you this memo?

DR. INSEL. No, I know the memo that this my--

MR. STEARNS. This is in 2005. Would that be fair--

DR. INSEL. To--

MR. STEARNS. You were asking for the unaccounted samples in 2005?

DR. INSEL. Did I use the word "unaccounted" in the memo?

MR. STEARNS. I am told by staff you were looking for the data that would help to answer where these unaccountable samples were, so that was over a year ago.

DR. INSEL. I--the memo that I sent, the e-mail I sent was that I wanted to find out what was sent to Pfizer and for the protocol--

MR. STEARNS. Well, Pfizer or someone else, not necessarily just Pfizer.

DR. INSEL. I am sorry, but in the memo, what I was asking specifically was the request about Pfizer.

MR. STEARNS. You said you wanted the number of samples and protocol.

DR. INSEL. I wanted the number of samples that would have been sent and the protocols that were involved in those shipments.

MR. STEARNS. Are you saying you weren't aware of that large number of unaccounted samples?

DR. INSEL. I am saying this to me is a very different topic. You are asking--so my understanding is that Dr. Sunderland had something like 16 protocols in which CSF was collected and many, many samples from across those protocols were sent to Pfizer. I wanted to get a listing of what was sent and what were the protocols that covered it.

MR. STEARNS. Well--

DR. INSEL. This is a question about one particular protocol done many, many years earlier that had to do with lithium which I must say is one of the smallest--

MR. STEARNS. Are you saying the graph is wrong? Yes or no.

DR. INSEL. I am--I would dispute the term "unaccounted for samples."

MR. STEARNS. Okay.

DR. INSEL. Because it makes it sound as if they are lost. They are not lost.

MR. STEARNS. Well, do you know what happened to them?

DR. INSEL. I can tell you that--you know, I--

MR. STEARNS. Can you tell me today what happened to all these samples?

DR. INSEL. I can tell you that Dr. Sunderland has a large number of CSF samples that are still stored at the NIH or through one of our contractors.

MR. STEARNS. In other words, today you can go back and identify all these samples today if we went out to NIH this morning?

DR. INSEL. This is really the core of what we have been talking about for the last hour. I specifically don't have an accounting for every sample. I have an accounting for the protocols. I have an accounting for the--

MR. STEARNS. But the people who work for you have that, is what you are saying?

DR. INSEL. Dr. Sunderland would have--I think could account for everything out there.

MR. STEARNS. But you said you can't manage unless you measure, but here it has been a year and you can't measure where these unaccounted samples are, so how can you manage it?

DR. INSEL. I am disputing your use of the word "unaccounted for." What I am telling you is that there are samples that remain under Dr. Sunderland's supervision. He is expected to be accountable for them.

MR. STEARNS. But he has not been accountable to you at this point?

DR. INSEL. I have not specifically asked the question of him, where are the five missing tubes of the many tens of thousands that you have from 1991.

MR. STEARNS. Let me go to the financial disclosure to the IRB. In part of that review process, Dr. Sunderland filed an exhibit which is 24, and the question which he checked off "no" said, "Have any investigators developed an equity or consultant relationship with a non-NIH source related to this protocol which might be considered a conflict of interest?" He checked off "no" and Dr. Rosenstein, your signature I guess is on here too. Do you think in light of what has happened here that Dr. Sunderland should have checked off "no." Is that in your mind satisfactory that he checked off "no" on this form?

DR. ROSENSTEIN. This is a question to me?

MR. STEARNS. Yes.

DR. ROSENSTEIN. I to this day don't know what the precise details of the relationship between Dr. Sunderland and Pfizer Pharmaceutical is so I can't answer that question definitively. I can say that if an investigator has a consultative relationship that is related to the research, then that should be checked off "yes."

MR. STEARNS. Well, let us just go back. Let us say you knew the facts today of his relationship with Pfizer and you had to put your signature down here. Would you have questioned Dr. Sunderland knowing what you know today about his relationship with Pfizer?

DR. ROSENSTEIN. Yes, I would have.

MR. STEARNS. And what would you have said to him?

DR. ROSENSTEIN. I would have asked for a description of the nature of the collaboration and would have brought that back to the full IRB.

MR. STEARNS. Would you allow him to vote to check off "no" on this form based upon what you know today?

DR. ROSENSTEIN. As you have heard, the samples that were sent to Pfizer were drawn from several different protocols.

MR. STEARNS. No, no, I mean just yes or no, if you knew back then what you know today about his relationship with Pfizer, would you have accepted him checking off "no" on this form?

DR. ROSENSTEIN. I would have raised the question at the IRB meeting, to ask for an explanation.

MR. STEARNS. And you would say Dr. Sunderland, is it possible that yes, you do have a disclosure and you should attach or append to this document your disclosure as what the form is requesting?

DR. ROSENSTEIN. Yes.

MR. STEARNS. So you would have done that knowing what you know today?

DR. ROSENSTEIN. Yes.

MR. STEARNS. So Dr. Insel, who is this Commissioned Corps? You are pretty much saying you can't do anything with Dr. Sunderland. You know that he is going to testify and you probably know he is probably going to take the Fifth. That is probably almost a 99 percent conclusion. I mean, I read his lawyer's comment here. He wouldn't come here unless the committee voted and he wants all his rights which I respect and he should have his rights. But I think it is pretty much a foregone conclusion he is going to take the Fifth, and with that in mind, you are saying you have no responsibility for his supervision or his employment or anything, that he has to report to this Commissioned Corps. Is that what you are saying today?

DR. INSEL. No. I am his supervisor because--

MR. STEARNS. Are you his supervisor?

DR. INSEL. As the Scientific Director, and I am in an acting capacity in that job for the next few weeks--

MR. STEARNS. Because you told Chairman Barton that you could not fire him, you could not do anything.

DR. INSEL. That is right.

MR. STEARNS. Now you are saying you are his supervisor?

DR. INSEL. And I have been--both things are true, so he is a member of the Commissioned Corps which means that he is essentially detailed to the NIH and hiring, firing, and promotion are done through the Corps, but the day-to-day supervision is done at the NIH.

MR. STEARNS. Like in a corporation, the hiring and firing is done through the personnel agency but the CEO can fire anybody he wants, and I assume that is what you are so--

DR. INSEL. Are you making a recommendation--

MR. STEARNS. The Commissioned Corps hires him but certainly if you felt his behavior was abhorrent, couldn't you make a recommendation that he be put on administrative leave?

DR. INSEL. I have done this. I have--there was an investigation and there was a recommendation that--

MR. STEARNS. What was your recommendation?

DR. INSEL. The recommendation to the Commissioned Corps was that we--based on the findings from the Office of Management Assessment, I was deeply disappointed and it appears to be--I think I said the violations were severe enough to merit termination were he in the civil service. I can't tell them what to do but I can tell them what we would do if he were--

MR. STEARNS. So you recommended to the Commissioned Corps that he be dismissed?

DR. INSEL. Yes.

MR. STEARNS. Okay. Thank you, Mr. Chairman.

MR. WHITFIELD. Mr. Ferguson.

MR. FERGUSON. Thank you, Mr. Chairman, and I appreciate your having this hearing.

I have some questions for Dr. Friedman actually. So Dr. Insel, you can just catch your breath for a few minutes. You have been getting a lot of questions this morning. Dr. Friedman, I didn't want you to feel that you were wasting your time this morning sitting here. But I want to further examine this relationship between Sunderland and Pfizer, and I read your testimony. You seem to know a little bit about that. So let us back up for a second. To your knowledge, did Pfizer contribute resources to the screening effort involved in these NIH samples?

DR. FRIEDMAN. They contributed a tremendous amount. There were at least half a dozen people that worked for years as well as enabling technology to be developed.

MR. FERGUSON. What kind of commercial products came from that?

DR. FRIEDMAN. No commercial products.

MR. FERGUSON. Zero?

DR. FRIEDMAN. To the best of my knowledge.

MR. FERGUSON. Could this type of research, this biomarker research that you have described, is it possible that this research would contribute to development of treatments for Alzheimer's?

DR. FRIEDMAN. It is viewed as being critical for development for treatments.

MR. FERGUSON. What happens to this kind of research? It gets published, what happens when someone conducts significant research that could have a real impact on--

DR. FRIEDMAN. That is above and beyond what I know about this particular collaboration.

MR. FERGUSON. In general.

DR. FRIEDMAN. In general, there is a point where it gets published and that usually follows patent applications but it's always dependent on the distribution of the intellectual property which is usually decided in advance. That is my basic understanding of it.

MR. FERGUSON. Who reads the publications?

DR. FRIEDMAN. Dr. Insel would be a good example of who reads the publications. Everyone in the scientific community does. It is open for input and that is one of the cornerstones of basic science.

MR. FERGUSON. So anybody in the health community could benefit from this research of it is published and--

DR. FRIEDMAN. As a matter of fact, I think that they could even benefit from the patent application information as well. There is a tremendous amount of information that is in the public domain and has been for years.

MR. FERGUSON. Okay. Now, we know that the rules for these consulting arrangements have changed since this particular instance that we are looking at today, that Dr. Zerhouni has told us about that, that the rules at NIH have changed regarding what is proper since this consultative relationship that Dr. Sunderland had with Pfizer, correct?

DR. FRIEDMAN. That is what I am hearing.

MR. FERGUSON. How would you characterize this relationship between Dr. Sunderland and Pfizer?

DR. FRIEDMAN. With regard to--

MR. FERGUSON. The activities, the consulting relationship that Dr. Sunderland had with Pfizer.

DR. FRIEDMAN. I really know very little--

MR. FERGUSON. You played a role in the initial--

DR. FRIEDMAN. What little I know about the consulting arrangement I have learned in the past few months being a part of this process. I am really not in a position to comment. I only know fragmentary information. I mean, if you want me to comment on information that is part of the committee report, it would be a totally uniformed--

MR. FERGUSON. Yes.

DR. FRIEDMAN. I will make one comment. From my experience of being part of several collaborations in different drug companies, direct compensation of $25,000 a year for the level of activity that Dr. Sunderland contributed to this project is modest at best.

MR. FERGUSON. How do these situations police themselves? Whose responsibility is it to police these--

DR. FRIEDMAN. To police them?

MR. FERGUSON. Yes.

DR. FRIEDMAN. From the point of view of a drug company?

MR. FERGUSON. Sure, or the point of view of any of us looking at these situations.

DR. FRIEDMAN. I wouldn't have any clue.

MR. FERGUSON. Well, would it be fair to say that a company in one of these situations is relying on the consultant to make a determination whether the relationship is appropriate or not?

DR. FRIEDMAN. It would be a guess if I answered that because I really have no knowledge of that.

MR. FERGUSON. What is your guess?

DR. FRIEDMAN. It is a fair assumption.

MR. FERGUSON. Okay. That is all I have. Thank you very much. I yield back.

MR. BURGESS. Will the gentleman yield for just a moment?

MR. FERGUSON. I would yield to Dr. Burgess.

MR. BURGESS. Dr. Friedman, you testified that the markers were in fact critical, the research into the biological markers in Alzheimer's was a critical part of that research?

DR. FRIEDMAN. I commented that the identification of these markers is critical to the development of Alzheimer's therapeutics from the point of view of large drug companies. That is part of, as you are well aware, the necessity of tracking any kind of efficacious response to a therapeutic over a reasonable period of time.

MR. BURGESS. And yesterday we heard testimony that the samples themselves were by virtue of having all of the genetic and clinical data on the people from whom they were recovered, that the samples themselves were extremely valuable. I guess what is troubling me is, in

1995, 1996 and 1997, you closed the study on an aspect of Alzheimer's that is critical to understand on samples that were widely acknowledged to be very valuable, and as a taxpayer and perhaps one day a consumer of whatever might be developed from this research at NIH, I am more troubled by that than anything else I have heard this morning, that we have a valuable field of study that we are basically just capping and walking away from and leaving in the refrigerator. I think--part of me says we should be grateful that someone picked this up and ran with it.

MR. FERGUSON. Are you looking for a response on that because I would like to reclaim my time?

MR. BURGESS. I was looking for a response from anyone who feels moved to respond to that.

DR. FRIEDMAN. I think Dr. Insel made the point which I will reiterate, good science never disappears. It is picked back up again by other investigators either in the intramural programs or extramural programs. People at drug companies--

MR. BURGESS. Since he is going to reclaim his time, you came perilously close to just disappearing back in the corner of that refrigerator when the study was capped in 1995 or 1996 before someone continued some type of research with those samples on biomarkers which we have admitted are critical to the understanding of Alzheimer's disease, on study samples that were very valuable because genetic contact and makeup of the study participants was known. I am just troubled that that might have not happened.

MR. FERGUSON. Now I am really going to reclaim my time. Just in closing, Mr. Chairman, the point I guess I am trying to draw out and confirm is that there can be great value, it seems to me, there can be great value to these collaborative arrangements and that is what it sounds like some of you have said this morning as well. There can be tremendous value to these collaborative arrangements but of course, the ends don't justify the means if they are not being done in a proper way, if they are not being disclosed in a proper way. To this point it seems like the policing for these arrangements has largely fallen to the researcher, the investigator themselves. That is probably why it is a good idea that Dr. Zerhouni is laying out some new guidelines. But we have to--and we all want the Camelot that you had described before, but it is going to be very important for us as we move forward, all of us together, to make sure that we don't lose the value of these collaborative efforts because of the enormous importance of the work that NIH is doing for the health of the Nation, and we just have to make sure that we are doing it in the right way and we have to make sure that we don't have this ends-justify-the-means mentality. I think maybe that is how I would sum up my feeling

on this, and I would suspect that may be true for others on the panel as well. Thank you, Mr. Chairman.

MR. WHITFIELD. Thank you. Just one other question, then we will get the second panel. Before I ask that question, did you have a unanimous-consent request, Ms. DeGette?

MS. DEGETTE. Yes, Mr. Chairman. I am sorry I missed the opening statements yesterday and I would ask unanimous consent that I be allowed to submit mine for the record. I would also ask unanimous consent that the record be kept open for this panel and the next panel and the panel yesterday for the requisite number of days for additional questions if members have--

MR. WHITFIELD. Without objection, so ordered. Dr. Friedman, you had testified that when you initiated this discussion, the initial discussion with Dr. Sunderland, that you were primarily focused on the transfer of the material and so forth and you were certainly not focused on meeting any ethical requirements at NIH. Is that true?

DR. FRIEDMAN. Well, it certainly wasn't my responsibility.

MR. WHITFIELD. Right, not your responsibility.

DR. FRIEDMAN. But it also wasn't true that I was focused on the transfer of the samples. I was focused on setting up, being participatory in setting up a collaboration.

MR. WHITFIELD. Collaboration. Okay. Now, I just want to read one excerpt to you. On Exhibit 41, if you would turn to that, this is a letter from Mr. Robert Muse, who I assume is the attorney for Dr. Sunderland, and in that exhibit it is a letter from Dr. Muse to Holly Beckerman-Jaffe, who is the Director of the NIH ethics office, and the reason I want to bring your attention to page 9 is that in this letter, Mr. Muse refers to you, and he said at the time of his inquiry, and I am assuming as you are exploring this coloration opportunity, Dr. Friedman was not aware that Dr. Sunderland had any prior association with Pfizer and that Dr. Sunderland promptly notified Dr. Friedman of this and stated that he would not be able to undertake any actions with regard to the collaboration until such activity was cleared and approved by NIH. Do you remember having that conversation with Mr. Muse?

DR. FRIEDMAN. I remember the conversation with Mr. Muse. I don't remember the exact details of that exchange but at no time was I involved in asking about what Dr. Sunderland's responsibilities were. That was his responsibility. Mine was to set up a collaboration and--

MR. WHITFIELD. But Dr. Sunderland did notify you that he would not be able to undertake any action with regard to the collaboration until such activity was cleared and approved by NIH?

DR. FRIEDMAN. What I recall is that Dr. Sunderland informed me that he needed to take care of these issues on his own before he could proceed.

MR. WHITFIELD. And then he went on to say in turn Dr. Friedman's goal was to make sure that the business, medical, and administrative people at NIH were fully informed.

DR. FRIEDMAN. That is certainly not true. In no way did I have any business responsibilities nor would Pfizer have given me those in any way.

MR. WHITFIELD. Okay. And as a matter of fact, Dr. Insel, I think you had previously stated that the policy even at that time was that if you were in collaboration with an outside entity and you had a consulting agreement with that entity, that that was not proper. Is that correct?

DR. INSEL. That is correct.

MR. WHITFIELD. At this time I would like to thank you all very much for your testimony and for being here today. I think this has been quite useful as NIH looks forward, moves forward to deal with these complicated issues and we want to thank you for the great work that you do at NIH and we look forward to continuing working with you as we make an effort to make sure it is a Camelot type of agency. Thank you very much. At this time I would like to call up the second panel, and on the second panel we have Dr. Trey Sunderland and Mrs. Karen Putnam, and if you all would please come forward and sit at the witness table, we would appreciate that. Dr. Trey Sunderland is the Chief of the Geriatric psychiatric branch at the National Institute of Mental Health, and Karen Putnam worked for Dr. Sunderland and is a former employee of the National Institute of Mental Health. They are here with us today pursuant to a subpoena. On May 24, 2006, the subcommittee invited these two individuals to voluntarily testify at this hearing but they declined. On June 3, 2006, Chairman Barton authorized subpoenas to be issued to compel their appearance, which were subsequently served. My understanding is that these witnesses will rely on their Constitutional right not to testify at today's hearing. I believe that this privilege which is the only basis upon which a witness may refuse to cooperate with an inquiry by the House should be personally exercised before the Members as we have done in the past. That is why we have insisted on the appearance of Dr. Sunderland and Mrs. Putnam today. Given the importance of their testimony to this subcommittee's fact-finding processes, I would hope that these individuals might reconsider their decision to invoke this Fifth Amendment right and cooperate with the subcommittee on this critically important investigation. Dr. Sunderland and Mrs. Putnam, you are aware that this subcommittee is holding an investigative hearing and in doing so it is the practice of the

subcommittee to take testimony under oath. Do any of you have any objection to testifying under oath today? Okay. As you know, under the rules of the House and the rules of the committee, you are entitled to have legal counsel. Do either of you have legal counsel with you today?

MS. PUTNAM. Yes, sir.

MR. WHITFIELD. And would you give the name of your legal counsel, please?

MR. SHURGLER. Your Honor, David Shurgler.

MR. WHITFIELD. David Shurgler.

MR. SHURGLER. I am licensed to practice in Washington, D.C.

MR. WHITFIELD. Thank you.

DR. SUNDERLAND. Robert Muse is my attorney.

MR. WHITFIELD. Robert Muse. Okay.

[Witnesses sworn]

MR. WHITFIELD. Thank you very much. At this time both of you are under oath, and I would ask either one at this time, do you have any opening statement that you would like to make, Dr. Sunderland?

DR. SUNDERLAND. No, sir.

MR. WHITFIELD. Dr. Putnam? Well, in that case, I would like to ask a question. I would recognize myself. Dr. Sunderland, according to records from Pfizer, the names and other privacy information of about 120 people, patients and volunteers who provided spinal fluid in National Institute of Mental Health studies, were inadvertently disclosed in 1999 shipments by your branch to Pfizer as part of one of the biomarker projects. Now, Dr. Sunderland, did you know about this disclosure and why this occurred?

DR. SUNDERLAND. Chairman, as you know, you have had correspondence from my attorney, Mr. Muse, on several issues and I respectfully decline to answer these questions or any further questions based on my Constitutional right.

MR. WHITFIELD. So you are refusing to answer the question on the basis of your Fifth Amendment rights, and is it your intent to invoke your Fifth Amendment rights in response to any other questions we may ask you today?

DR. SUNDERLAND. It is with great regret that I say yes to that question.

MR. WHITFIELD. Then you are excused from the witness table at this time but I advise that you remain subject to the process of the committee and that if the committee's need is such, then we may recall you.

DR. SUNDERLAND. Yes, sir. Thank you.

MR. WHITFIELD. Dr. Putnam, my next question for you is this. Mrs. Putnam, according to NIH records involving you, there were 2,132 vials of spinal fluid shipped to Pfizer in connection with a known biomarker

project representing samples from 538 subjects and about 14 different protocols but there were about 1,100 vials shipped in connection with the unknown biomarkers or discovery research project. Do you know if there is data showing how many subjects are represented in those samples and from what protocol numbers?

MS. PUTNAM. Upon the advice of my attorney, I will assert my Fifth Amendment privileges and respectfully decline to answer.

MR. WHITFIELD. So Ms. Putnam, you are refusing to answer the question on the basis of the protections afforded to you under the Fifth Amendment of the U.S. Constitution?

MS. PUTNAM. Yes.

MR. WHITFIELD. And you would invoke that Fifth Amendment right on any additional questions that we may ask you today?

MS. PUTNAM. Yes, sir.

MR. WHITFIELD. Then you also are excused from the witness table at this time but I would advise you that you remain subject to the process of the committee and that if the committee's need is such, we may recall you at some future time. Thank you. At this time I would like to call up the single witness in the third panel, and that is Dr. Michael Gottesman, who is the Deputy Director for Intramural Research at the National Institute of Health. Dr. Gottesman, thank you very much for being with us today. We appreciate your time. We look forward to your testimony. As you know, this is an investigating oversight committee hearing and it is our process to take testimony under oath. Do you have any objection to testifying under oath today?

DR. GOTTESMAN. No, I do not.

MR. WHITFIELD. And do you have legal counsel with you today?

DR. GOTTESMAN. No, I do not.

[Witness sworn]

MR. WHITFIELD. You are now under oath, and we recognize you for your 5 minute opening statement.

STATEMENT OF MICHAEL M. GOTTESMAN, M.D., DEPUTY DIRECTOR FOR INTRAMURAL RESEARCH, NATIONAL INSTITUTES OF HEALTH, U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES

DR. GOTTESMAN. Thank you, Mr. Chairman, Mr. Stupak and members of the subcommittee.

I am Dr. Michael Gottesman, the Deputy Director for Intramural Research at the National Institutes of Health, an agency with the U.S. Department of Health and Human Services. I am responsible for oversight and coordination of intramural research, training, and

technology transfer activities conducted within the laboratories of the 22 intramural research programs of the NIH. So in that sense, I am that person who oversees both the research and the policies that keep NIH researchers out of trouble.

The intramural program represents about 10 percent of the total NIH budget, or $2.8 billion in fiscal year 2006. Our 6,000 intramural scientists work in an environment where creativity is encouraged and cutting-edge research is the norm. Discoveries such as the first effective chemotherapy for childhood leukemia and Hodgkin's disease and the use of AZT to treat AIDS were developed in the clinical center at the NIH.

The NIH intramural research program could not succeed nor could any scientific endeavor without collaborative interactions between our scientists and scientific investigators in academic research institutions and in private industry. Such collaborations are encouraged as you have heard. Without them, the pathway to discovery would likely be slowed by innumerable obstacles and many of our greatest research achievements might not have occurred.

Of course, policies intended to facilitate collaborations between Federal and private-sector researchers must be firmly grounded in ethical principles. The NIH leadership was reminded of the importance of this principle 2 years ago by this subcommittee, and in your recommendations, we realize that there were many areas in which we could improve our oversight. Your recommendations prompted NIH and the Department of Health and Human Services to revisit and dramatically strengthen ethics regulations, as you know, in 2005. New department regulations addressed vulnerabilities of the NIH ethics system by completely banning all personal or outside consulting by NIH scientists with pharmaceutical and biotechnology companies. Private outside consulting on subjects that are the same or similar to an employee's official duties has always been prohibited, as you have heard, even under previous regulations. The events under consideration at today's hearing occurred before these new regulations were issued, the ones absolutely banning consulting arrangements. The subcommittee has understandable concerns about the transfer of human biological samples from NIH to the private sector in connection with the consulting arrangement. NIH shares these concerns.

First and foremost, we want to know if important biological samples were transmitted without adequate controls and if human subject protection requirements were met. Second, we want to be sure that our internal controls on biological samples are consistent with all requirements including the regulation governing outside or personal activities.

Regardless of the outcome of the multiple reviews concerning this matter, I would like to be perfectly clear about NIH's position. Any attempt to illegally profit from official research activities, especially where human biological materials are involved, is totally unacceptable. Engaging in such an activity is a violation of NIH core ethical principles past and present. We cannot tolerate such behavior since it undermines the credibility of NIH as an unbiased source of scientific information. I am told that the material in question, spinal fluid taken from Alzheimer's disease patients, was provided by an NIH intramural scientist to a pharmaceutical company. This transfer of human tissue samples has raised numerous issues and concerns including the adequate protection of the rights of individuals who participate in clinical trials, alleged conflict of interest, and intellectual-property issues. These areas of oversight involve complex regulations and interactions that need to be clarified, and I think Dr. Insel's chart was just the beginning of the complexity of the issue.

What can we do to assure that problems such as this do not recur? In addition to the reforms implemented in our ethics program, we are enhancing policies pertaining to the handling of human tissue samples and related intellectual property. While sharing such materials facilitates and accelerates the scientific process, it is also clear that additional protections must be in place when scientists share tissue samples including blood, serum or, in this case, cerebrospinal spinal fluid. Accordingly, after reviewing our policies and procedures regarding the transfer of such materials, we determined that further clarification is necessary and we are taking the following steps.

Number one, NIH will provide guidance to investigators on the different mechanisms including MTAs, letters of collaboration, and cooperative research and development agreements available for entering into collaborations and transferring materials outside of the NIH, and we will require that all transfers of samples derived from human subjects must use a written mechanism so there will be no transfer without a written mechanism. NIH will clarify that in cases involving the transfer of material derived from human subjects, all such written agreements must be accompanied by more-rigorous checks and balances including the review and approval by senior leadership at the relevant institute, so an investigator on his own cannot arrange to transfer these samples.

NIH has initiated a comprehensive review of policies across NIH involving MTAs to determine if additional requirements are necessary in the case of MTAs that do not involve the transfer of material derived from human participants. I just want to point out that most of our transfers are of laboratory-derived research tools, pieces of DNA or cell

lines or antibodies, things like that, that don't directly affect human subjects or clinical research.

NIH has also reviewed its policies governing the use of stored human tissue samples. Stored human tissue samples if identifiable by codes or other identifiers are considered human subjects under applicable Federal regulations. Research uses of previously collected and stored human samples when intramural research program investigators can personally identify the sources must be prospectively reviewed and approved by an institution review board. This is not negotiable. IRBs are charged by Federal regulation 45 CFR part 46 with reviewing research protocols to protect the rights and safeguard the welfare of research participants. When reviewing a proposed new research use of stored samples, an IRB will consider the original research use and carefully consider the informed-consent document in order to determine if the new use is consistent with the original protocol. We believe the process for reviewing uses of stored samples must be clear and rigorous. In order to assure that all NIH intramural research program researchers understand the requirements for the research use of stored samples, the following steps will be or have been taken.

A memorandum has been sent to all intramural clinical researchers, clinical directors, and scientific directors clarifying the oversight requirements for the collection and research use of human samples, data and specimens. The clinical center's Medical Executive Committee, which consists of the clinical directors and some other leading scientists in all the institutes, implemented procedures to assure that all clinical center protocols receive continuing NIH IRB review and approval as long as research analyses using coded samples continues. So if a protocol is closed but the samples are still valuable, in order to use those samples you need continuing review and approval by an IRB.

NIH will modify its standard MTA form to include language indicating that the transfer of either coded or identifiable samples has been reviewed by an IRB or exempt from IRB review pursuant to 45 CFR 46. All research protocols in which intramural researchers intend to collect and store human samples, specimens, or data must include a detailed description of the intended use of the samples including any proposed future use, even after termination of the protocol. Consent documents must include relevant language. While we cannot anticipate all prospective uses, we want to ensure that research participants have as much information as possible on how their own material will be maintained and used.

While these new rules will establish conditions to prevent the recurrence of the problems we have heard about today, in order to be fully successful we must be sure that our staff is fully educated about

these rules, that they have the administrative support needed to keep up with the additional paperwork, and we have heard about this issue of overloading people with bureaucratic obstacles and delaying research. This can be addressed with administrative support and these people can also provide expert advice because these are complex regulations. And if the rules are knowingly violated, there will have to be consequences.

Science is an ongoing process that requires constant review and adaptation. The same is true for NIH's programs that manage the research enterprise. Many of our adaptations result from internal review. Some ensue from external oversight such as the work of this subcommittee. In either case, NIH leadership understands we must be responsive.

Thank you for this opportunity, Mr. Chairman. I would be pleased to answer questions.

[The prepared statement of Michael M. Gottesman, M.D. follows:]

PREPARED STATEMENT OF MICHAEL M. GOTTESMAN, M.D., DEPUTY DIRECTOR FOR INTRAMURAL RESEARCH, NATIONAL INSTITUTES OF HEALTH, U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES

Good morning Mr. Chairman, Mr. Stupak, and Members of the Subcommittee. I am Dr. Michael Gottesman, the Deputy Director for Intramural Research at the National Institutes of Health (NIH), an agency within the U.S. Department of Health and Human Services (HHS). I am responsible for oversight and coordination of intramural research, training, and technology transfer activities conducted within the laboratories of the 22 intramural programs of the NIH. The intramural program represents about 10 percent of the total NIH budget, or $2.8 billion in Fiscal Year 2006. Our 6000 intramural scientists work in an environment where creativity is encouraged and cutting edge research is the norm.

The intramural research program provides unique opportunities and resources to encourage important high-risk, high impact scientific inquiries that may be difficult to pursue in the private sector or academia. Intramural laboratories are regularly subjected to rigorous outside reviews.

The NIH Clinical Center is the focal point of the intramural enterprise, where laboratory scientists and clinicians work in close physical and intellectual proximity, providing a unique cauldron for translational and clinical research, with the cost of patient participation covered by the NIH budget. The first chemotherapeutic cures for childhood leukemia and Hodgkin's disease, and the first use of AZT to treat AIDS, resulted from research done at the Clinical Center, the largest research hospital in the country. Of the 19 scientists with medical degrees who have won Nobel Prizes in Medicine in the past 20 years, nine were trained in the intramural program at NIH.

The NIH intramural research program could not succeed – nor could any scientific endeavor – without collaborative interactions between our scientists and investigators in academic research institutions and private industry in the course of their official work. Such collaborations are encouraged. Without them, the pathway to discovery would likely be slowed by innumerable obstacles and many of our greatest research achievements might not have occurred.

Of course, policies intended to facilitate collaborations between federal and private sector researchers must be firmly grounded in ethical principles. The NIH's leadership was reminded of the importance of this requirement two years ago by this

Subcommittee's investigation of consulting arrangements between intramural scientists and companies in the pharmaceutical and biotechnology industries. Your oversight review prompted NIH and HHS to revisit and dramatically strengthen ethics regulations in 2005.

New HHS regulations addressed vulnerabilities in the NIH's ethics system by completely banning all personal or outside consulting by NIH scientists with pharmaceutical and biotechnology companies. Private outside consulting on subjects that are the same as or similar to an employee's official duties has always been prohibited, even under previous regulations. The events under consideration at today's hearing occurred before these new regulations were issued. It is a sensitive matter that is still the subject of ongoing review.

The events are connected to research on Alzheimer's disease, specifically attempts to identify biomarkers that identify the early presence of the disease. This research is one of the most important areas of investigation regarding Alzheimer's disease and should be pursued with vigor. But the quest for biomarkers by NIH must be conducted according to Federal rules pertaining to human subjects protection, intellectual property, and conflicts of interest.

As I understand it, the Subcommittee has specific concerns about the transfer of human biological samples from NIH to the private sector in connection with a consulting arrangement. NIH shares these concerns.

First and foremost, we want to know if important biological samples were transmitted without adequate controls and if human subject protection requirements were met.

Second, we want to be sure that our internal controls on biological samples support the application and enforcement of all requirements, including the regulation governing outside or personal activities.

Regardless of the outcome of the multiple reviews concerning this matter, I want to be perfectly clear about NIH's position. Any attempt to illegally profit from official research activities, especially where human biological samples are involved, is totally unacceptable. Engaging in such an activity is a violation of NIH's core ethical principles, past and present. We can not tolerate such behavior.

I am told that the material in question – spinal fluid taken from Alzheimer's disease patients – was provided by a NIH intramural scientist to a pharmaceutical company. This transfer of human tissue samples has raised numerous issues and concerns, including the adequate protection of the rights of individuals who participate in clinical trials, alleged conflict of interest, and intellectual property issues. These areas of oversight involve complex regulations and interactions that need to be clarified.

With this principle in mind, on August 25, 2005, HHS, with the concurrence of the Office of Government Ethics, published a final rule governing standards of ethical conduct for NIH employees. The new regulation contains the following additional provisions:

- All NIH employees are now prohibited from engaging in outside employment with pharmaceutical companies and biotechnology companies.
- The extent to which the most senior NIH employees may hold certain types of stock and other financial interests is severely limited.
- The number of employees required to disclose financial interests is significantly expanded.

In addition to the reforms implemented in our ethics program, we are enhancing policies pertaining to the handling of human tissue samples and related intellectual property. While sharing such materials facilitates and accelerates the scientific process, it is also clear that additional protections must be in place when scientists share human tissue samples, such as blood, serum, or as in this case, cerebrospinal fluid. Accordingly, after reviewing our policies and procedures regarding the transfer of such materials, we determined that further clarification is necessary. In order that NIH

employees understand that formal mechanisms such as Material Transfer Agreements (MTAs) are required when human research materials are transferred, we are taking the following steps:

- NIH will provide additional guidance to investigators on the different mechanisms available for entering into collaborations and transferring materials outside of the NIH. While we thought that the current rules were clear to most scientists, we think it is necessary to clarify that a MTA should be used when transferring materials. Scientists should use research collaborative agreements, or Cooperative Research and Development Agreements (CRADAs), when entering into research collaborations with industry.
- NIH will require that all transfers of samples derived from human subjects must involve a written mechanism – MTA, CRADA, letter of collaboration, or other agreement. Such agreements must be in writing to ensure compliance with all requirements regarding human subjects protections. Further, the use of written mechanisms will permit NIH to track the sharing of clinical samples with outside entities, and monitor compliance with the policy.
- NIH will clarify that in cases involving the transfer of material derived from human subjects, all such written agreements must be accompanied by more rigorous checks and balances, including the review and approval by senior leadership at the relevant Institute.
- NIH has initiated a comprehensive review of policies across NIH involving MTAs to determine if additional requirements are necessary in the case of MTAs that do not involve the transfer of material derived from human participants. NIH policy requires the widespread dissemination of research tools. It is not clear, however, that such enhanced protections should be required for all materials, such as laboratory-produced DNA samples, cell lines, and antibodies, whose main function is to accelerate research. A further analysis is necessary to inform policy development in this area.

NIH has also reviewed its policies governing the use of stored human tissue samples. Stored human tissue samples, if identifiable by codes or other identifiers, are considered "human subjects" under applicable Federal regulations. The intramural research program's human research protection program functions under a Federal-Wide Assurance (FWA) with the HHS Office for Human Research Protections (OHRP). Its FWA commits the intramural program to conduct its human subjects research activities consistent with acceptable ethical principles and in compliance with 45 CFR part 46, the regulation governing the protection of human subjects in research. I am responsible for implementing the FWA, and the Office of Human Subjects Research (OHSR) within the Office of Intramural Research serves this purpose.

Research uses of previously collected and stored human samples, when intramural research program investigators can personally identify the sources, must be prospectively reviewed and approved by an Institutional Review Board (IRB). IRBs are charged by federal regulation (45 CFR part 46) with reviewing research protocols from the vantage point of protecting the rights and safeguarding the welfare of the research participants. When reviewing a proposed new research use of stored samples, an IRB will consider the original research use and carefully consider the informed consent document in order to determine if the new use is consistent with the original protocol. If the research is subject to regulation by the Food and Drug Administration (FDA) (for example, if an investigational diagnostic test is being studied), then the IRB would also apply FDA regulations. We believe the process for reviewing new uses of stored samples must be clear and rigorous. In order to assure that all NIH intramural research program researchers understand the requirements for the research use of stored samples, the following steps have been or will be taken:

- A memorandum has been sent to all intramural clinical researchers, clinical directors, and scientific directors clarifying the oversight requirements for the collection and research use of human samples, data and specimens.
- The Clinical Center's Medical Executive Committee implemented procedures to assure that all Clinical Center protocols receive continuing NIH IRB review and approval as long as research analyses using coded samples continues.
- NIH will modify its standard MTA form to include language indicating that the transfer of either coded or identifiable samples has been reviewed by an IRB or is exempt from IRB review pursuant to 45 CFR part 46 as determined by OHSR. This step will assist technology transfer staff in determining whether the scientist has adhered to human subjects requirements.
- All research protocols in which intramural researchers intend to collect and store human samples, specimens, or data must include a description of the intended use of the samples; how the samples will be tracked; how they will be stored; what will happen to the samples at the completion of the protocol; what circumstances would prompt the investigator to report to the IRB loss or destruction of samples, and any proposed future use (i.e., use after termination of the protocol). Consent documents must include relevant language. While we cannot anticipate all prospective uses, we want to ensure that research participants have as much information as possible on how their own material will be maintained and used.

These steps will help ensure that investigators fully understand NIH requirements for the research use of previously collected, stored human samples, and that proposals for such uses must be approved by an IRB and by OHSR.

Science is an ongoing process that requires constant review and adaptation. The same is true for NIH's programs that manage the research enterprise. Many of our adaptations result from internal review. Some ensue from external oversight, such as the work of this Subcommittee. In either case, NIH's leadership understands we must be responsive.

Sometimes the problems identified by internal and external oversight are systemic, but sometimes they result from individual behavior. To the extent NIH identifies systemic issues, we will take appropriate action. In the case of individual misconduct, we will seek remediation, including dismissal, where warranted.

Thank you for this opportunity, Mr. Chairman. I will be pleased to answer your questions.

MR. WHITFIELD. Dr. Gottesman, thank you very much for your testimony, for being here today. First of all, as the Deputy Director for Intramural Research, I would like for you to explain as if you were addressing maybe a rotary club in Leesburg, Virginia, exactly the process that you need to go through if one of your research scientists at, say, the National Institute of Mental Health, came to you with a collaborative agreement and wanted to enter into a collaborative agreement with some third party. Could you just kind of walk us through the steps that would be necessary to clear that?

DR. GOTTESMAN. Yes. First of all, when you said come to me, you mean come to the appropriate authority at the institute?

MR. WHITFIELD. Yes.

DR. GOTTESMAN. So when we engage in cooperative research and development agreements or so-called CRADAs which are the most

formal of our agreements with companies, sometimes the agreement is initiated by an investigator who is aware of interests that accompany or somebody else may have in the product. Oftentimes it results from advertising. We actually have adverse research opportunities at the NIH and most often if there is an opportunity to develop a specific idea or a product, our technology development people will meet with the scientists, understand the scope of the project and then advertise that there are opportunities for other companies and then people apply for that opportunity. They are interviewed entirely by the technology development coordinators within the institute. At this point the investigator is not involved in the discussions in terms of negotiations except as an advisor on the scientific aspects of the research. After some discussions, a document is drawn up which describes in detail the nature of the collaboration and we require--there is a whole set of rules that cover what we will allow and what we won't allow. For example, NIH does not do research for hire. If a company wants us to do research for them, we generally won't do that unless it is clear that that is jointly desirable from the point of view of moving science forward. There is a bunch of rules and there is a policy that covers that. I am sure the committee is aware of that. After those discussions, there is review internally, a document which includes a conflict of interest review in which questions are asked about whether the scientists involved in the research have any outside personal activities with the organization, and if they respond that they don't and our review indicates that that is correct and we do--the deputy ethics counselors at each of the institutes does review using Internet searches and so on.

MR. WHITFIELD. So they have to file a form that--

DR. GOTTESMAN. There is an extensive document which is the CRADA application form which includes something called a conflict-of-interest evaluation. It is not only a statement by the scientist but it is also a request--there is a process in which the institute actually looks into that statement. As you know, we are developing a better electronic system for tracking all of the different activities of our scientists and that will be an enormous help in researching whether or not there is or is not conflict of interest. If the institute is interested in moving forward, the recommendation goes to a central committee, which is the cooperative Research and Development Committee, which reports to me. There is a chair, and that committee reviews and determines whether the CRADA is in keeping with NIH CRADA policy, makes a recommendation. Sometimes some of the points of the CRADA need to be negotiated. And then that goes back to the institute. It gets renegotiated. It comes back for discussion. Our legal counsel, the Office of Technology Transfer, signs off and I actually sign off centrally as DDIR on all those

documents. So it is a very formal, very careful process to guarantee that there is no conflict of interest, that the research is in the interests of the people of this country and that it is scientifically important to move ahead.

MR. WHITFIELD. The institute from which it comes is involved, the Office of Intramural Research, and the Office of Technology Transfer is involved. Did I miss any other--

DR. GOTTESMAN. Well, my office, the Office of Intramural Research, the Office of Technology Transfer, the technology development coordinators within the institutes, the committee, the CRADA committee. Many people. And the deputy ethics counselor who reviews the conflict-of-interest statement. So I would say from my point of view, this is a model system. It obviously takes some time to negotiate these agreements and it is possible during that interim period if there is a partner who is anxious to get research going to have a letter of collaboration which precedes a cooperative research and development agreement to allow research to move forward.

MR. WHITFIELD. Are there additional safeguards put into these collaborative agreements when human tissue samples are involved or not?

DR. GOTTESMAN. Only to the extent that we have human subjects regulations that I have mentioned that kick in. We have a requirement that if there is a CRADA involved in the study, that the IRB be informed about the CRADA, know how the partners are and so on. So we are beginning to make these connections between the different oversight parts of the NIH.

MR. WHITFIELD. So the consent forms that donors sign in providing human tissue samples to the institute, they disclose suppose in a rather broad way how this material can be used?

DR. GOTTESMAN. So, Mr. Chairman, if you are speaking about the consents that the patients--

MR. WHITFIELD. Yes.

DR. GOTTESMAN. Yes. So the process of informed consent has been one of the key features of the development human subjects' protections. I would say that in the early 1990s when many of the protocols were being conducted that we are talking about here, the consent forms were not very specific and in fact, in reviewing for this hearing I looked at some of the consents that were used in this case and it is clear that the patients were being--that subjects that were being asked to sign off very generally on use of materials. That kind of general language would not be allowed in the current environment.

MR. WHITFIELD. Now, there has been some discussion today about the necessity or the need for a central protocol that would extend

throughout NIH, particularly relating to human specimen repositories and so forth, but the impression that I get from testimony is that every individual institute already has pretty stringent protocol for tracking this. Is there a real need for a broad policy throughout NIH or is it better to have each institute take care of that?

DR. GOTTESMAN. So by tradition, scientists have always controlled their own research activities and resources in the sense that they by virtue of the requirements under our research integrity program are responsible for keeping adequate records for storing samples in an appropriate way, for using these samples under all appropriate rules and regulations. This is part--Dr. Insel mentioned that some of the system is based on trust, and traditionally at the NIH and in all scientific institutions, the individual scientific investigator has had that responsibility. One of the ways in which we are dealing with whether or not those responsibilities are being exercised appropriately is to make sure that samples aren't used for purposes other than the original intended purpose under the approved protocol by requiring all the different steps that I have mentioned.

I think probably what is most important is that NIH has been thinking very hard about ways in which we could optimize the use of these samples. As you point out and as many of committee members have pointed out, these are very valuable materials. They are unique in the sense that at no time or place will that individual ever be able to give that sample again if you are looking at a longitudinal study and somebody is being studied over 10 or 20 years and many of the NIH studies are long-term studies. The sample that goes back 20 years as a predictor of a disease to come is a very important sample and not easily reproduced although you could reproduce the whole study.

So we really want to be sure that these samples are used appropriately, and one of the things that NIH has been working on in keeping with actually the desire of the whole Federal government to create a much more electronic database for medical and clinical issues is, you know, what does it take to make the system entirely electronic so it is easily queried and you can use materials easily, and we started actually by developing a clinical research information system which took about 5 years and is now in place in the clinical center which tracks all patients' medical records, their test results and their images, their X-rays and so on so that it is possible now, and I invite you all to visit the clinical center, to stand at a patient's bedside and get electronic descriptions of what they are doing. This is the kind of futuristic view of medicine I think NIH is actually taken the lead in this. Each of the institutes is developing in their own way clinical research tools to be able to analyze their specific clinical trials, and as it turns out--I had mentioned we have 22

intramural programs. About 17 of them do clinical research. And the type of clinical research differs substantially amongst the institutes so each has different needs and a few different protocols are being developed. I just spoke to one of our scientific directors who spent 4 years developing a data set, a tracking program for clinical samples, clinical trials, clinical questions that are being asked in the institute within one of the institutes and we talked about the feasibility of making that more generally available and I think that will begin to happen.

I think we are still up against a bit of a technical problem. The number of samples involved is overwhelming and we are not talking about, you know, putting bar codes on them as they come in. We are talking about going back 20, sometimes 30 years and we are talking about millions of samples at the NIH. So this is a big task but I think it is a laudable goal both from the oversight point of view and also because what it does is, it makes available these potential data sets to people who have a new idea for research.

MR. WHITFIELD. My time has expired. I recognize Ms. DeGette.

MS. DEGETTE. Thank you very much, Mr. Chairman. Dr. Gottesman, I want to ask you some questions that I also talked to Dr. Insel about and the first one is, that--and by the way, I applaud your determination to raise the bar here. I think it is important and I think we would all agree. And the Chairman was also alluding to what I talked to Dr. Insel about which is, we are getting ready to do NIH reauthorization in this committee and Dr. Zerhouni wants more centralized decision-making that would then take the inter-institute cooperation to a higher level which I think is a good idea.

But my question is, it seems to me that the physical tracking of these tissue samples, and heaven knows what else that we are keeping at NIH, is at a very rudimentary level, and if we are going to have more cross-institute cooperation, which I think is really the cutting edge of medical research, how on Earth can we hope to achieve those laudable goals if we don't really make a push for much better cataloging and much better cross-referencing?

DR. GOTTESMAN. I agree with you, and I think that--

MS. DEGETTE. Well, how can we do it? Do you--

DR. GOTTESMAN. Well, I mean, I have a variety of authorities and I also have ability to persuade people above and beyond my authority. So in terms of tracking samples as the institutional official human subjects' research, I can require that we know that every sample has been approved by an IRB before it gets used, before it gets sent out and so on. In terms of the requirement that there be scientific tracking programs, electronic databases, there I use my persuasive powers to make it clear that these are important scientific as well as management issues for our

scientific directors. We hold them responsible. I delegate to them responsibility for tracking human samples, making sure they are properly used, and under that authority, I can ask them to make sure that they know where the samples are.

MS. DEGETTE. But do you intend to have some kind of a standard protocol throughout the institutes that other people can access?

DR. GOTTESMAN. Well, as I said, the needs of each of the institutes are somewhat different. The type of protocols that are carried on at NIMH and the Cancer Institute are really quite different in kind.

MS. DEGETTE. Right, but what I am saying is, if you have a bunch of tissue samples at those two institutes, just cataloging what you have got there and what people are using, that is not different.

DR. GOTTESMAN. No. So there is a term in computer networking called interoperability.

MS. DEGETTE. Yes, I know that.

DR. GOTTESMAN. And if we let 1,000 flowers bloom and we say everybody needs to develop a system for tracking and we don't require that those systems talk to each other, then we have a problem.

MS. DEGETTE. Sir, this is exactly what I am saying.

DR. GOTTESMAN. The advantage we have at NIH is, we have a central clinical center which is really supported by taps on each of the institutes. That clinical center has a database that I mentioned which includes all the different--

MS. DEGETTE. And how long has that been in place?

DR. GOTTESMAN. It is about a little over a year.

MS. DEGETTE. So that was not in place when the--

DR. GOTTESMAN. No, no.

MS. DEGETTE. Would that system have--right now if something like this happened now, would that system stop it?

DR. GOTTESMAN. No, that system doesn't track clinical samples but--

MS. DEGETTE. So what are we going to do to stop it?

DR. GOTTESMAN. In order for an investigator to be able to use that system with respect to their clinical samples, it would need to be interoperable so that the fact that we have invested so much in the central system will really force the interoperability of the other systems. They won't be useful to our scientists unless they can interact with the central system. So what I am saying is that--

MS. DEGETTE. Okay. You know, I--

DR. GOTTESMAN. --we are heading in the right direction.

MS. DEGETTE. Okay. I may follow up with some more questions because I frankly don't understand what you are saying. I want to talk to you about this chart. I am sure you have seen this, the one that Dr. Insel

gave us, and I think it is all swell that we have all of these cross checks and so on, but as I was sitting here looking at this chart, if somebody wanted to take some tissue samples and just go outside the chart around the arrows, there is nothing in here that would prevent that from happening. If someone just wanted to do that--I mean, within the institutes--I think this is great, the IRBs, the board of scientific counselors, the Office of Technology Transfer and so on. If someone just wanted to take those tissue samples out, go to a pharmaceutical company and profit on the side, this system would not have a safeguard. Wouldn't you agree?

DR. GOTTESMAN. Yes. So what you are saying is that if somebody--if we say what the rules are and somebody willfully breaks those rules by not reporting--

MS. DEGETTE. Right, which is what happened in this case.

DR. GOTTESMAN. Or taking samples and not reporting that they have used them for that purpose.

MS. DEGETTE. Right.

DR. GOTTESMAN. There is nothing in the current system that would prevent that.

MS. DEGETTE. Right. Even in this beefed-up system.

DR. GOTTESMAN. And I am hard pressed in any kind of enforcement process to be able to answer how to prevent an individual from doing that except to say that there needs to be some sort of auditing function tied in to all of these processes so that we know maybe not for every person who is involved but on a representative basis how it is that the system is working.

MS. DEGETTE. Well, I have two suggestions. Number one is, if you beef up your tissue tracking system which we can talk about more later, then even if somebody is going out beyond that, if they take the issue samples out, you have got some kind of computer model that would say well, where did they go, they didn't go over to another institute or something, that would be a double check. The second--because the evidence is gone. I used to do a lot of criminal work in practicing law, and if somebody went to the evidence vault at the police department and checked the evidence out, then it didn't show up where it was supposed to show up, then you knew there was a problem. That is very simplistic but it is the same type of thing. And the second suggestion I would make is that if there is somebody who is so guilty of such gross malfeasance as in this case, one might want to think about how the personnel rules at the NIH could be modified so they could be fired before 2 years were up, because he is still there even after this happened. I don't know if you want to comment on any of that.

DR. GOTTESMAN. Well, the only comment I would make and I know there is confusion about the various appointment authorities at the NIH, civil service versus Commissioned Corps, the Commissioned Corps is a separate authority. It is a uniform service and they run their operations similar to the uniform military code and they make determinations about hiring and firing people and we do not control that at NIH.

MS. DEGETTE. And we might want to look at that. My next question is around the informed consent that the people who originally donated these tissues for, and again, Mr. Chairman, I would ask unanimous consent to submit the consent form for the record. And I am sure you have seen this. You might even have it--you are being handed it. Okay. This is the original consent form that was used for Dr. Molchan's study, and it seems to me--I looked it over and it seems to me fairly specific--you were talking earlier about you really need to look at the informed consent and have it be specific and have it be full, and I support that completely. But it looks to me like in this situation, the informed consent was quite specific and quite thorough for the research study that Dr. Molchan was saying she was conducting. Wouldn't you agree with me?

DR. GOTTESMAN. Well, in one sense, yes, but let me point out something in the informed consent that perhaps you didn't notice which changes the tone of it. At the end of the first paragraph, "We hope to obtain information on changes in hormones and brain chemicals"--that is very broad—"that occur in Alzheimer's disease and in depression."--my goodness, that is huge—"as well as clues to the mechanism of the action of lithium." It makes it sort of clear that anything goes, and that is why I think an IRB in looking at this currently would just say this is not acceptable--you can't ask somebody to sign off on something like--

MS. DEGETTE. All right. So even though there is a lot in there, it is that phrase that--

DR. GOTTESMAN. It is that phrase.

MS. DEGETTE. So it is an interesting dichotomy, isn't it, because on the one hand you want to have an informed consent that is specific exactly to the research study but then on the other hand, what do you do later on if somebody wants to make a secondary use of these tissues? Do you have--and frankly, as Dr. Insel pointed out, with Alzheimer's or many other diseases, it is likely the donor might already be dead. So how are you going to go back--do you think you go back and get a second informed consent or do you think somehow you draft this form so it is both specific enough to deal with this research study but broad enough to let you use the tissues later?

DR. GOTTESMAN. Right. So we have two new requirements I think that will clarify that point. The first is that is absolutely essential in

writing up a new protocol to specify not only the intent of the protocol, what the study is about, but what will happen with the samples--how they will be stored, how long they will be kept, what will happen if somebody wishes to use them for another purpose, would there be re-consent, would there not be and so on. And the second point has to do with the requirement for IRB review. If the IRB reviews--for example, if these had gone before an IRB for re-review, the IRB would have looked at the original consent. It might have said well, this is so general that maybe patients understood that this was going to happen with their samples but in fact there is an issue over time that suggests that no one could have conceived of the kind of sophisticated analysis that we are doing now 13, 14, 15 years ago and that therefore patients need to be identified. In fact, Dr. Sunderland has patients who he has followed over the years and are still alive and were involved in some of these protocols and maybe they would conclude, although I don't know for sure, that there would be a need for re-consent. They can either say the risk is very small and therefore the new research can move forward, they can waive consent based on the fact that they believe that there is no risk to the patients and the original consent covered the area, or they can request that there be re-consent, and we re-consent patients all the time.

MS. DEGETTE. You know, the other thing, and I know it is always on a case-by-case basis, but the subjects of this study, even though that statement was broad, it said this study is researching this. It didn't say anything about and I give consent for future. I mean, it may be what you might want to look at in some cases is having people give specific consent for this study and then developing a secondary consent form that you could have and you can use these tissues for future use.

DR. GOTTESMAN. Well, I would be very delighted to continue this discussion with you because these are issues that the NIH is struggling with and the entire research community is struggling with.

MS. DEGETTE. Thank you very much, Mr. Chairman.

MR. WHITFIELD. Dr. Gottesman, just as a follow-up on this consent, do you really think that most patients care that much about how their samples are going to be utilized?

DR. GOTTESMAN. Well, there have been studies done on this issue, and many patients who are participants in clinical research studies, human subjects research studies, are actually enormously altruistic and they believe--they trust the scientists who are working. They want them to be able to use the samples to help them or to help somebody else and I think maybe the majority of people who participate in clinical research feel that way. On the other hand, sometimes they are uninformed about the potential risks to them. If a discovery is made about some aspect of their physiology that could affect their insurability or their employability,

those are really important risks that need to be considered and we would like to be able to reassure people that even if they can't think of problems, that we will be thinking about these things and making sure that samples are not used for purposes that could put them at any risk.

MR. WHITFIELD. Just a couple of other questions. In your testimony you stated the NIH will accomplish three things. One, you will provide additional guidance to investigations on material transfers; two, you will require that all transfers of samples derived from human subjects must involve putting it in writing; three, the NIH will clarify that in cases involving human transferred material, that there will be review and approval by senior leadership at the relevant institute. Now, is that already being accomplished or do you have a time guideline for this?

DR. GOTTESMAN. Right. So because this involves changes in our technology transfer program, I have more direct authority over the human subjects' part because I'm the institutional official. So we are convening a group of administrators and scientists to consider all aspects of material transfer at the NIH, transfer from laboratories as well as clinical samples. I will promise this committee that those aspects that we promise to do will certainly take place, but there may be other changes in our policy as well, and we want to be able to release not piecemeal but altogether the policy on material transfer at the NIH that everybody understands, that everyone adheres to.

MR. WHITFIELD. And do you have a general time guideline on that?

DR. GOTTESMAN. I think we can probably accomplish this within a couple of months.

MR. WHITFIELD. Now, one other question. We have talked a lot about the collaborative research agreements and we talked about the material transfer agreements, and not being familiar with either one of them I would like to just ask you this question. We have on Exhibit #2, there is a material transfer agreement by the National Institutes of Health, the provider is Trey Sunderland, the recipient is Pfizer, which is the case that we have all been focused on, and in paragraph three when it talks about how the research material will be used, it says, "Research to identify and validate protein markers associated with Alzheimer's disease." Now, is that--from your background as a scientist, your experience, is that too broad or is that adequate or--

DR. GOTTESMAN. Well, I think the problem is that this is a material transfer agreement that is not just transferring materials. It is specifying a collaborative agreement. And I think that under normal circumstances if this had been thoroughly reviewed by a technology development coordinator, the conclusion would have been that this is not an appropriate transfer agreement, transfer mechanism that--I always prefer to see CRADAs because, as I told you, the system is very formalized and

works well. But it could have been done under a collaborative agreement with a company, but that has to be signed off by the technology people and the senior leadership at the NIH. So the issue here is not whether this is specific or not specific. It is that it is not an appropriate vehicle to transfer the materials.

MR. WHITFIELD. Okay. So it is not an appropriate vehicle?

DR. GOTTESMAN. I don't believe so, no.

MR. WHITFIELD. Well, I will make one other comment, then I will recognize Mr. Stupak here. I want to ask you to do something for us. I would like for you to work with the National Institute of Mental Health to report to us on all of the underlying data that Dr. Sunderland should have on the GPB shipments to Pfizer that would break down by sample in each shipment and the protocol numbers so that we can get a more clear understanding of the specifics of that because in the conversations that we have had with the various people at NIH, we still are a little bit--we are not sure precisely on the specifics of this. In some of the memos I have seen, I know that the National Institute of Mental Health referred to 11 percent here and eight percent here was used and whatever. We would just like to get a more clear understanding of the exact shipments, the protocol numbers and so forth, and how much was utilized as it relates to Pfizer with Dr. Sunderland.

DR. GOTTESMAN. Mr. Chairman, we will do the best we can to get the information. As you know, there is an ongoing investigation and we have been generally instructed by counsel to try not to confuse the different investigations, but I certainly would like to get you that information and I will work with the people at NIH and see if we can make that happen.

MR. WHITFIELD. And Exhibit 26 may provide some help to you on that as well, so we can give you a copy of that before you go. We will get a copy to you before you go. At this time I recognize Mr. Stupak.

MR. STUPAK. Thank you. Dr. Gottesman, how long have you been at NIH?

DR. GOTTESMAN. I have been at NIH 31 years.

MR. STUPAK. Okay. In this new position as--

DR. GOTTESMAN. In my current position?

MR. STUPAK. Yes.

DR. GOTTESMAN. Almost 13 years.

MR. STUPAK. Thirteen years. Has this issue ever arose before about use of samples and scientists outside?

DR. GOTTESMAN. There are a couple different issues. The use of samples for research purposes is a constant area of discussion at the NIH and we are constantly making policy and the policy, as I said to Congresswoman DeGette, is a kind of moving target.

MR. STUPAK. Well, it seems like there was policy for handling hazardous materials or samples but not for this here. Why was--

DR. GOTTESMAN. Well, the NIH policy I think is pretty clear and that is dictated by all the requirements for human subjects' research, that if there is a closed protocol and that somebody wants to use a sample, they need to get permission from the IRB to use that sample. There is an oversight responsibility.

MR. STUPAK. So here there should have been an IRB and then was it 46 CFR 45, was that--that should have been followed?

DR. GOTTESMAN. Right. That is the controlling legislation, yes.

MR. STUPAK. And that should have been followed, right?

DR. GOTTESMAN. That should have been followed. What was not made clear earlier this morning was that actually some of these protocols are still open. Some of the samples were sent under open protocols and some of them were sent under closed protocols. There were a total of 16 protocols.

MR. STUPAK. Right.

DR. GOTTESMAN. And 11 of them had been closed prior to the period when the samples were sent.

MR. STUPAK. So--

DR. GOTTESMAN. Five of them are still open and undergoing continuous IRB review.

MR. STUPAK. Okay. And then the IRB--it is my understanding Dr. Sunderland was head of the IRB, right?

DR. GOTTESMAN. At one--during this period he was the chair of the IRB, yes.

MR. STUPAK. So who would he get permission from then to--

DR. GOTTESMAN. The original review and approval of the protocols that allowed the samples to be collected were done with an IRB chair who was another person. He was recused--

MR. STUPAK. Well, the original samples, I guess there are no questions there but then they were moved outside for commercial gain, if he is head of the IRB, who would he get his permission from?

DR. GOTTESMAN. So in the course of reviewing the human subjects' materials, we found that in some cases Dr. Sunderland did sign off during the continuing review process on protocols in which he was a co-investigator.

MR. STUPAK. So he should have received permission or someone sign off--

DR. GOTTESMAN. Someone else should have done that. That was--

MR. STUPAK. With this new flow chart, will that work? I mean, really. I know we had some comments about this. You are talking about

this flow chart here, and how does that make--like if I am head of the IRB, where do I go then to get my permission?

DR. GOTTESMAN. I mean, this is one of the very basic principles of the conduct of any human affair. If it is your business which is being reviewed, you don't sit as a chairman on the committee that reviews it.

MR. STUPAK. So really what it comes down to, it is not this colorful chart. It really comes down to the integrity of the individual?

DR. GOTTESMAN. Well, and the institution. I mean, that should not have been allowed.

MR. STUPAK. Right. But in order to bypass the safeguards that any institution puts in whether it is NIH or Congress, it still boils down to the individual, whether or not they are going to follow that protocol, whether they are willing to take that risk and what is the benefit to them, almost like a cost-benefit analysis in a way.

DR. GOTTESMAN. Well, as I said to Congresswoman DeGette, it is based on trust but at the same point, we can develop oversight mechanisms that reduce the likelihood that any one individual will absolutely violate the rules.

MR. STUPAK. Sure. You indicated in your testimony to the Chairman here that there is still ongoing investigation in this matter. Is that true?

DR. GOTTESMAN. Yes, that is true.

MR. STUPAK. What area is the ongoing investigation still going on?

DR. GOTTESMAN. Well, I mean, Dr. Insel mentioned this morning that the AG and the Justice Department have shown some interest in this case and I don't know the state of--

MR. STUPAK. It is nothing else that NIH is doing other than if Justice asks for something--

DR. GOTTESMAN. Well--

MR. STUPAK. --you will provide them with the information?

DR. GOTTESMAN. Following a meeting that I had with the counsel for this committee, when I was made aware of what I thought were problems with the human protections issues, I initiated through my own office and through the Office of Human Subjects Research a paper investigation of the various paperwork--

MR. STUPAK. That investigation is done though, right?

DR. GOTTESMAN. It is not completed yet but it is in progress and we have already made a report to the Office of Human Research Protections about it.

MR. STUPAK. You said you met with House counsel here or committee counsel, I should say, excuse me. So were you part of the team at NIH that put together the information that the committee requested?

DR. GOTTESMAN. My involvement was actually minimal. I mean, NIH separates the oversight of the science from the management issues related to disciplining scientists, for example, but I was involved at one step, which was--there was a committee put together to determine whether in fact there was an overlap between the outside activity and the official duty activity.

MR. STUPAK. Right.

DR. GOTTESMAN. It was a committee of scientists.

MR. STUPAK. That is a little different than what I am asking. This committee had a hearing in 2004 on this issue. We followed it up. Myself and Mr. Whitfield, Chairman Barton, Mr. Dingell, signed a letter in June of 2005 asking for certain information. Were you part of the NIH team that helped put together the response?

DR. GOTTESMAN. Yes. Actually, our legislative people came to my office and gave me the questions and asked if I could help get some of the information about what was existing NIH policy. The initial questions were about storage of samples, freezer stability, and so on, and what were policies concerning oversight, and we provided information about human subjects and material transfer.

MR. STUPAK. And how about the follow-up letter of January 4, 2006, and January 26, 2006, by this committee, were you part of that team that put together those answers?

DR. GOTTESMAN. I am not sure what those refer to but--

MR. STUPAK. Is there any question as to whether or not the human tissue samples collected by NIH scientists using government resources are property of the Federal government?

DR. GOTTESMAN. There is no question they are property of the--

MR. STUPAK. Under what authority do you make that statement?

DR. GOTTESMAN. The legal authority. I think there is probably some place in the legal code--I mean, this is something that every scientist who comes to NIH is told: Every product of your research here belongs to the Federal government.

MR. STUPAK. Everyone has testified to that but no one can point us to the authority.

DR. GOTTESMAN. I can certainly have our legal people research it and get you an answer to that.

MR. STUPAK. Okay. I mean, the issue came up yesterday too. It was asked a couple times. At the NIH, is there a policy regarding data that is over 5 years old? You know, there has been some testimony that Dr. Sunderland indicated that everything was purged and therefore the data wasn't available anymore.

DR. GOTTESMAN. So our research integrity policy which has to do with what scientists are expected to do in terms of maintaining their

notebooks and their samples and so on states that samples need to be kept for 5 to 7 years. The new requirements from the Office of Research Integrity, which is part of the Department of Health and Human Services, are fully 7 years and we are in the process--and that is a new requirement--we are in the process of aligning our requirement with that requirement. So the department requirement will be retention of materials, data, samples for 7 years.

MR. STUPAK. Then what happens to it after that?

DR. GOTTESMAN. Then they can be destroyed or--they can't be used for purposes other than the intended purpose, but they can certainly be destroyed.

MR. STUPAK. In this case, with the lithium study, was any of that destroyed, any of that data or research information destroyed?

DR. GOTTESMAN. I have no idea. I know at some point there was an e-mail which stated that the material had been purged, the information had been purged but I don't know if that actually happened.

MR. STUPAK. Let me ask you this question, if I may. The rules at NIH concerning consulting between like NIH and scientists and private industry I am sure have changed since Dr. Sunderland. I am concerned, however, that the abuses of the system from which Dr. Sunderland profited were not only due to lack of regulation but in fact the lack of enforcement of this regulation. How can you assure this committee that there is now an appropriate level of actual enforcement other than this chart? I like the chart but it doesn't do much for us.

DR. GOTTESMAN. Right. Well, one of the points I made in my testimony is, it is not sufficient to make policy. You have to be sure that people understand it, understand the reason for it, have support in order to be able to carry out, and know that there are consequences if they don't follow it. And I think that the current environment at NIH is much more sensitive to the need for oversight and management. Some mention was made about the culture of scientists and the culture of administrators. I think one of the things that I have been working on for sure is convincing scientists that management of science is just as important as the conduct of their science.

MR. STUPAK. Your deputy ethics counselor, that is in place now?

DR. GOTTESMAN. Yes, so what this represents is--

MR. STUPAK. Let me ask you this. I don't mean to interrupt but time is running short. Does this chart, does it apply to the Corps? We have had testimony that you can't do things about Dr. Sunderland because he is part of the Corps. Would this all apply to the Corps also?

DR. GOTTESMAN. Yes. Anyone who is in the Corps who works at NIH is subject to all the same rules and regulations.

MR. STUPAK. So if I violate whether I am in the Corps or whether I am at NIMH but not part of the Corps, if I violate one of these rules I could be terminated, I don't need the Corps permission then?

DR. GOTTESMAN. No. The problem is that if you are appointed in the Corps, the Corps makes the determination about whether you can be terminated.

MR. STUPAK. But yet this so-called accountability chart, if you will, or whatever you want to call it, your chart here, this is going to apply to the Corps?

DR. GOTTESMAN. The requirements for people who work at the NIH are the same whether they are appointed--

MR. STUPAK. Corps or civil service or independent--

DR. GOTTESMAN. The decision about hiring and firing is made by the Corps, not by the NIH. That is the issue.

MR. STUPAK. I just want to make sure the Corps is going to accept this.

DR. GOTTESMAN. They do and they will.

MR. STUPAK. Okay. Thank you, Mr. Chairman.

MR. WHITFIELD. One other question, Dr. Gottesman. In response to Mr. Stupak, you talked about human tissue samples can be destroyed after 5 to 7 years. Is that mandatory or is that just--

DR. GOTTESMAN. No. I guess it is an expectation that materials--we don't expect them to be retained for more than 7 years. In many cases for the clinical samples that obviously continue to be valuable samples, they should be maintained and I think it an interesting issue. Most of our scientists will continue to keep them, hoard them in their freezers and hoping that they will be useful at some future time.

MR. WHITFIELD. Yes, because you can freeze these fluid samples for I guess forever, right?

DR. GOTTESMAN. Well, the issue about actually what the lifetime is of these samples in the freezer is a scientific question and I think has not been resolved, at least to my satisfaction.

MR. WHITFIELD. It depends on what you are going to use them for and so forth. Okay. Dr. Gottesman, thank you very much for your testimony. We appreciate your being here today and we look forward to working with you as we move forward to maintain the integrity and the sterling reputation of NIH. Thank you. This hearing is adjourned.

[Whereupon, at 12:55 p.m., the subcommittee was adjourned.]

RESPONSE FOR THE RECORD OF THOMAS R. INSEL, M.D., DIRECTOR, NATIONAL INSTITUTE OF MENTAL HEALTH, NATIONAL INSTITUTES OF HEALTH, U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES

DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

National Institutes of Health
National Institute of Mental Health
6001 Executive Blvd.
Bethesda, Maryland 20892

September 12, 2006

The Honorable Ed Whitfield
Chairman, Subcommittee on
Oversight and Investigations
Committee on Energy and Commerce
House of Representatives
Washington, DC 20515

Dear Mr. Whitfield:

Thank you for your continuing interest in the National Institutes of Health (NIH). Below are my responses to each of the questions Mr. Stupak raises following up on my testimony from the June 14 Subcommittee on Oversight and Investigations hearing, entitled "Human Tissue Samples: NIH Research Policies and Practices."

1. Dr. Insel, at our June 14 hearing, you indicated that you had advised the Commissioned Corps regarding Dr. Sunderland that a civil service member having behaved in a manner similar to his would be terminated. Given that his actions warrant his termination by your analysis, but that he is nevertheless still at the NIMH, what steps have you taken to ensure that he cannot do further harm to the Institute?

As Director of the National Institute of Mental Health (NIMH), I have used my authority to restrict Dr. Sunderland's activities. In addition, I have changed his duty assignment to have him working directly with my office and to restrict his access to resources under investigation in our extramural program rather than continuing in his previous post in the Geriatric Psychiatry Branch.

2. Does the relationship between the Commissioned Corps and NIH undermine your supervisory capacity? If you do not have the authority to terminate any researcher from the Corps, even one with abuses so egregious as Dr. Sunderland, does this compromise your oversight ability?

There are currently only eight Commissioned Corps officers at the NIMH, representing roughly 1 percent of our employees. Generally, these officers are exemplary employees with a deep commitment to the mission of the Institute and the values of the Public Health Service. Indeed, over the past 25 years, I know of no earlier case in which the NIMH has recommended termination to the Commissioned Corps. While one might expect that a management environment where a supervisor does not have the authority to terminate an employee would

limit that supervisor's oversight, this has not, to my knowledge, ever been a problem for either the Corps or the NIH. In Dr. Sunderland's case, while the ultimate discipline rests with the Corps, there are many aspects of his position that can be managed by his NIH supervisor, as noted in the response to question #1.

3. You indicated at the hearing that the NIMH was considering a number of policy changes. Yet there were policies in place meant to prevent researchers from entering into conflicts of interest, and one still occurred, mostly because those policies were not followed. Aside from the new rules, regulations, and chains of command you introduced to the committee, what methods of oversight and enforcement are you considering lo ensure that these rules are actually enforced.

As Dr. Zerhouni explained in an earlier hearing, the new NIH ethics rules require extensive disclosure and impose new limits on financial interests. They also prohibit paid consulting (but not official duty collaborative work) with industry and establish additional approval requirements for outside activities. NIH has also engaged in a comprehensive training effort to explain the new rules.

At the June 14 hearing, Dr. Gottesman and I described a number of changes made to ensure closer scrutiny of collaborations with outside entities, including a requirement that all collaborations and Material Transfer Agreements involving clinical samples be reviewed by an Institutional Review Board. In addition, at NIMH, we are engaged in a complete inventory of clinical samples and their associated protocols and collaborations. As you suggest in your question, these policies need enforcement, and there must be consequences for failure to follow them. As NIMH director, I am committed to ensuring that all appropriate staff fully understand and comply with these new regulations.

4. How can the NIMH ensure the new rules and regulations will be enforced, when the violator is a high ranking scientist such as Dr. Sunderland?

Although the rules apply to everyone, they are most strict for those of highest rank, such as Institute Directors and those who report directly to them. This point is important: in matters of ethics, the Institute's reputation rests squarely on the integrity of its high-ranking scientists. Enforcement requires monitoring and discipline and both apply irrespective of rank. Monitoring occurs via our new ethics system, which requires extensive reporting and approvals for outside activities and our new policies requiring the annual review of research involving clinical samples. Discipline for conflict-of-interest violations can range from reprimands to suspensions to termination for NIH employees, with additional potential for criminal prosecution.

5. Given what you know now about the correlation between the shipment of human tissue samples and the consulting payments, would you say that Dr. Sunderland not only violated conflict of interest policies, but violated his fiduciary duties to NIMH, and to his patients and volunteer subjects?

It is my understanding that Dr. Sunderland's case remains under investigation. While there is an ongoing investigation, it would be inappropriate for me to venture an opinion about any violation of his fiduciary responsibilities.

6. Putting aside the apparent conflict of interest that existed with Dr. Sunderland in his dealings with Pfizer, I'm also concerned about the extent to which NIMH benefited from the supposedly scientifically valuable aspects of the collaboration. According to the agreement, NIMH was to provide samples and linked clinical data to Pfizer, which would perform assays on the samples. Can you demonstrate for the committee that NIMH has received the results associated with these assays? Where is the data?

Dr. Sunderland's official collaboration with Pfizer was entirely appropriate as an NIMH/industry collaboration. Pfizer performed high-quality assays of beta-amyloid (1-42) and tau, candidate protein biomarkers in the CSF of patients at risk for Alzheimer's disease. The results of this collaboration are a matter of public record. Most notable was a lead paper in the *Journal of the American Medical Association* (April 23, 2003), yielding one of the first and arguably best biomarkers for diagnosing Alzheimer's in its earliest stages when treatment may be most useful. Additional data from this collaboration have reported the use of beta-amyloid and tau values in people with a genetic predisposition to Alzheimer's (*Biological Psychiatry*, July 2004), have demonstrated the stability of these measures (*Dementia and Geriatric Cognitive Disorders*, May 2006) and have formed the basis of an upcoming critical review on the practical value of biomarkers for the diagnosis of Alzheimer's disease (*Journal of Geriatric Psychiatry and Neurology*, September 2006). NIMH believes that this collaboration, in which Pfizer performed hundreds of expensive assays at no charge to the Government, was good for the American public, especially for those with family members at risk for Alzheimer's disease. Data from clinical studies of the Geriatric Psychiatry Branch reside on a Government server at NIH. Pfizer has returned all unused samples to the NIMH.

I hope this information is helpful. Please let me know if I can be of further assistance.

Sincerely yours,

Thomas R. Insel, M.D.
Director

RESPONSE FOR THE RECORD OF WILLIAM FITZSIMMONS, EXECUTIVE OFFICER, NATIONAL INSTITUTE OF MENTAL HEALTH,, NATIONAL INSTITUTES OF HEALTH, U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES

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September 12, 2006

The Honorable Ed Whitfield
Chairman, Subcommittee on
Oversight and Investigations
Committee on Energy and Commerce
House of Representatives
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Dear Mr. Whitfield.

Please find enclosed my answers to Mr. Stupak's questions from the June 14 Subcommittee on Oversight and Investigations hearing, entitled "Human Tissue Samples: NIH Research Policies and Practices."

I hope this information is helpful to you. Please let me know if you have any further questions.

Sincerely yours,

William T. Fitzsimmons
Executive Officer, NIMH

Enclosure

NIMH
National Institute
of Mental Health

1. Please clarify what was required of Dr. Sunderland by the Technology Transfer Office and NIMH at the time in which he executed the MTA involving the CSF samples. We were told by some of our witnesses that Dr. Sunderland did not have authority to sign the MTA himself. But in response to a number of questions submitted by the subcommittee on February 16, 2006, you submitted the following: "It is important to note, however, that whether Dr. Sunderland was authorized to sign the MTA and whether he was permitted by NIH to send the material (with or without a signed MTA) are two separate questions. NIH policy at the time of the transfer did not require an MTA or other written agreement to transfer the material." Are you stating that Dr. Sunderland was permitted to transfer any type of material without any sort of written agreement?

Response: My understanding is that NIH policy in place at the time encouraged scientists to use MTAs for exchanging materials with other scientists but that such transfers did not require any written agreement. It has been the policy of NIMH since early 2006 that all transfers of tissue samples to individuals outside of NIH be effected under a formal written agreement.

2. What is the purpose of the entire approval system if an MH scientist is not required to go through the process? Why would any researcher seek approval for any action?

Response: We believe the focus at the time was to allow flexibility to NIH's intramural research scientists. While it was acceptable for an NIH scientist to exchange materials on an informal basis, any written agreement that might bind the NIH required review and approval.

3. If it was indeed the case that Dr. Sunderland was not required to use a written agreement when transferring samples to an outside agent, when and how has that policy changed?

Response: It has been the policy within NIMH since early 2006 that all transfers of tissue samples to individuals outside the NIH must be effected under a formal agreement, such as an MTA, a Collaborative Research and Development Agreement (CRADA), Clinical Trial Agreement, or Collaboration Agreement, with Institution Review Board (IRB) approval also required in some cases.

4. Was an MTA the proper mechanism for Dr. Sunderland to use in his collaboration with Pfizer? Assuming he did decide to use an MTA, would this need to be reviewed by your office?

Response: Because Dr. Sunderland was sending tissue samples to Pfizer as part of a research collaboration, a CRADA or some other similar type of formal collaboration agreement would have been the more appropriate mechanism for Dr. Sunderland to use. Use of a CRADA would have automatically triggered a conflict-of-interest review by me, in my role as the Institute's Deputy Ethics Counselor. As it was, the MTA signed in 1998 did not require review by my office.

5. Why was the MTA not received by the Scientific Director until a year after the samples were transferred?

The answer to this is not totally clear. Our records show that this MTA was one of three agreements retroactively signed by the Scientific Director in early 1999, after an office clerk discovered various documents requiring the Scientific Director's approval and brought them to him for signature.

6. What was the method by which your office would keep track of leave taken by scientists for private consulting? How did your office determine whether or not an NIH scientist was using the appropriate leave during such activity?

Response: My office did not traditionally keep track of such leave. The outside activity approval request form in use between 1982 and 2005 simply required an employee to state whether or not the work to be done would be performed outside of usual work hours and to indicate the hours or days of absence (i.e., requiring leave). This form was routed through the employee's supervisor, and it was then expected that normal supervisory oversight--the supervisor had to approve or disapprove leave requests--would be sufficient to ensure the leave involved was properly recorded. Recent revisions to the outside activity approval request form address this issue more specifically, asking what form of leave is being requested. In addition, a copy of the leave request and approval must be included in the outside activity request packet sent to my office for approval.

7. What actions could your office take if a transfer was found to have carried out without the proper referrals?

Response: NIMH scientists are encouraged to self-report breaches of violations of the policies governing human subjects research. In cases where NIMH investigators were discovered, either through self-report or another mechanism, to have transferred samples improperly several actions could be taken depending on the nature of the violation. As an improper transfer of samples would generally be considered an adverse event, a report to the IRB and the NIMH Clinical Director would ordinarily be made. In addition, the Office of the NIMH Scientific Director and the NIH Office of Human Subjects Research (OHSR), and possibly the NIH Deputy Director for Intramural Research and the Office of Human Research Protections (OHRP), could be notified. Other possible actions that might be taken include a reprimand of the investigator by the IRB, consent changes and/or modification, and suspension or termination of the protocol. In addition, the investigator could be subjected to disciplinary action by NIMH and/or review by the Medical Executive Committee of the Clinical Research Center

8. Why didn't the involvement of Oxford Glycosciences as an unnamed third party trigger any further scrutiny from the Office of Technology Transfer? Should it have?

Response: The Institute's Office of Technology Transfer appears not to have taken notice of the MTA's reference to a third party collaborator. If such language were included in a proposed MTA today, the Institute normally would ask for the third party to also enter into an agreement. However, MTA agreements do sometimes permit the distribution of materials to an organization's subsidiaries and affiliates without them being named. Other third party

collaborators and partners, however, should be named and asked to enter into a separate agreement with the NIH, or be required in writing to be bound by the same terms and conditions, when the collaborator provides NIH materials to them.

9. What actions does the NIMH take to ensure that human subjects are properly protected? Does the approval process involve any scrutiny of coding or encryption to ensure that the identities of the subjects are protected?

Response: The NIMH has a comprehensive human subjects protections program that operates within an overarching human subjects protection system administered by the NIH Office of Human Subjects Research (OHSR). The two major components of the NIMH Intramural Research Program protections system are the NIMH IRB and the Office of the Clinical Director. Consistent with Federal regulations, the NIMH IRB conducts initial and ongoing ethical reviews of all clinical research activities conducted within the Intramural Research Program of the NIMH (approximately 100 research protocols). Protocols undergo scientific review and human subjects protections pre-review before being sent to the IRB for formal review. The IRB meets twice a month and includes scientists and clinicians from within and outside the NIMH, as well as a bioethicist and community lay members. The IRB stipulates a variety of subject protections (e.g., study screening and exclusion criteria, safety monitoring plans, rules for stopping the protocol, follow-up reporting mechanisms, and specific steps to be taken in the event of an adverse event).

In addition, the NIMH Office of the Clinical Director has created multiple mechanisms to ensure the protections of our research subjects. The most important of these initiatives was the creation of the Centralized Office for Recruitment and Evaluation (CORE). This is an office of a dozen seasoned clinicians (master-level nurses and social workers), supervised by a senior nurse and two physicians who are charged with the safety and protection of NIMH research subjects. They perform a variety of functions on behalf of our subjects including the following: study screening assessments to identify appropriate participants and rule out high-risk or unstable subjects; informed consent monitoring; assessment of decision-making capacity for subjects with questionable capacity to provide informed consent; and ongoing clinical monitoring of subjects to identify cases of clinical instability at the earliest times.

Finally, the Office of the Clinical Director has worked diligently to create a culture in which the safety of our research subjects is deeply valued and enforced. The NIH and NIMH require ethics training for all clinical investigators, and we offer extensive training in research bioethics and human subjects protections.

With respect to protecting the identity of research subjects, multiple safeguards are in place. All clinical research protocols and associated consent forms are required to address the issues of confidentiality and privacy of research subjects. The conduct of research is required to be in compliance with the Federal Privacy Act and NIH policies regarding data with personal identifiers. Specific procedures vary according to the research requirements dictated by the protocol. In most cases, research data are "coded" in that a research subject's data are assigned a unique identifier that can be linked with the subject's name if necessary for data analysis or for follow-up clinical purposes. Any code lists or data collected and retrieved by personal identifiers are maintained as required by the Privacy Act, e.g., password protected or under lock

and key. Data are also occasionally stripped of all identifiers ("anonymized") although that typically limits the subsequent research utility of these data. In all cases, the principal investigator is ultimately responsible for adequate safeguarding of the research data. In cases of breach of confidentiality or compromised privacy, an inquiry is done, and the breach and/or potential violation reported as applicable to the subject, IRB, OHSR, OHRP, the Clinical Director, the Clinical Research Center, etc., depending on the nature of the violation..

RESPONSE FOR THE RECORD OF MICHAEL M. GOTTESMAN, M.D., DEPUTY DIRECTOR FOR INTRAMURAL RESEARCH, NATIONAL INSTITUTES OF HEALTH, U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

National Institutes of Health
Bethesda, Maryland 20892
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SEP 1 8 2006

The Honorable Edward Whitfield
Chairman, Subcommittee on
Oversight and Investigations
Committee on Energy and Commerce
United States House of Representatives
Washington, DC 20515

Dear Mr. Whitfield:

Please find enclosed my answers to Mr. Stupak's follow-up questions from the June 14 Subcommittee on Oversight and Investigations hearing, entitled "Human Tissue Samples: NIH Research Policies and Practices."

I hope this information is helpful to you. Please let me know if you have any further questions.

Sincerely yours,

Michael M. Gottesman, M.D.
Deputy Director for Intramural Research, NIH

Enclosure

1. In responses to questions from Chairman Whitfield and Representative Degette, you stated that the type of general language regarding the use of samples on informed consent forms used by NIH in the past would not be permitted on present consent forms, and gave a few examples of what would now need to be provided. Could you explain the reason for this change?

The way in which human samples can be analyzed in the laboratory has changed dramatically over the past 10 years. Analyses that were undreamed of 10 years ago, such as complete DNA sequence analysis, sophisticated analyses of protein content and protein modifications (also known as proteomics) and analysis for a host of biomarkers are now possible. Thus, an informed consent document from several years ago that included a general statement about samples being used for research purposes would not likely be considered today to include appropriate information for the patient about the kinds of information that could be obtained from the sample and the possible risk to the patient should such information become available to an insurer, an employer, or a relative. In keeping with changing requirements to assure human subjects protections, NIH IRBs are becoming more insistent on informed consent documents making much clearer what samples may be used so that a patient can make an informed decision about whether to allow anticipated uses, including relatively unrestricted use.

2. Even with the new criteria for implied consent, it seems that the Institutional Review Board still may not have the proper mechanisms for ensuring human subjects protection when samples are shared with private entities. Does the IRB consider the original implied consent forms when determining whether outside collaborations involving human tissue samples are appropriate?

For some informed consents of several years ago, the intent of the consent is clear, and if the test or research that is going to be done satisfies this intent and does not expose the patient to excess risk, an IRB might decide to waive consent requirements for the new research to proceed. This is why it is important that use of samples or data of human subjects, as 45 C.F.R.46 prescribes, be overseen by an IRB or the NIH Office of Human Subjects of Research. In the case of collaborations involving human subjects, the NIH IRB reviews whether the proposed new research is consistent with the original informed consent and considers if it imposes any additional risk to the subject before deciding whether to waive consent requirements for the new activity. In general, any new use of samples of human subjects would need to be reviewed by an IRB which would use the criteria listed above and other regulatory standards found in Part 46 to determine whether re-consent of human subjects is necessary.

3. The incident with Dr. Sunderland appears to be a case of an individual with a position of power within NIH going around the rules and regulations in order to enter into an inappropriate relationship with an outside agent, and benefiting personally from government property. In your response to a question from Representative Degette, you acknowledged that even with new regulations, such abuse would be difficult to prevent without some sort of "auditing function." Could you elaborate on what you meant by that? Does the NIH have any plans to ensure that the conduct of all NIH researchers is properly monitored?

NIH is improving its oversight of researchers in the three areas: ethics, technology transfer, and human subjects protections in the following ways:

a. Unless an exception is granted, no outside activities with significantly affected organizations (SAOs)(generally, biotechnology, pharmaceutical and medical device companies) are allowed for NIH employees. All clinical investigators on clinical protocols must report all investments in significantly affected organizations (SAOs) and the most senior NIH employees cannot have investments in SAOs above the de minimis ($15,000), except in very limited circumstances. How does NIH know that employees are following these stringent policies? The NIH is strengthening the monitoring of its ethics program. In addition to creating a compliance division within the NIH Ethics Office, the NIH has completed the roll-out of phase one of an enterprise system that will link together several data bases so that we can more readily and consistently flag potential conflicts. The NIH is also exploring other methods to assure compliance with the rules.

b. A committee has been formed, co-chaired by the Director of the Office of Technology Transfer and the Deputy Director for Intramural Research, to evaluate existing documents and policies related to technology transfer. This committee is reviewing various means to assure that human samples cannot be transferred without approval by an appropriate high level authority, such as a Scientific Director, within an institute. Some transfers are part of collaborative agreements or Cooperative Research and Development Agreements (CRADAs) which must be reviewed by an investigator's supervisor (for collaborative agreements) or by several high level officials (for CRADAs)). All employees will be educated about the requirements for transfer of human samples. It is the intent of NIH to develop a biorepository system that keeps track of human samples obtained as a result of human subjects research so that all uses of such samples can be tracked. A committee has been established to determine the best way to carry out this process for samples obtained in the future and for documenting samples obtained in the past.

c. Human subjects protection oversight at the NIH requires that use of all human subject samples be under continuing review of an IRB or overseen by the NIH Office of Human Subjects of Research. This requirement will be monitored by Clinical Directors within each IC, and will be reinforced through an educational program for all employees.

4. How can the NIH ensure that new rules and regulations will be enforced, even if the violator is a high-ranking scientist such as Dr. Sunderland?

Rules and regulations are always subject to individual violation. Four approaches are being taken to reduce the risk that this occurs at NIH to a very low level: (1) Education of all NIH staff about the requirements of the rules and regulations; (2) Provision of administrative support to reduce the burden of implementing these rules and regulations; (3) Clear disciplinary action if

rules and regulations are violated; and (4) Monitoring as indicated above to reduce the time required to detect violations.

5. The Office of Technology Transfer has informed the committee that there is a question as to whether or not Dr. Sunderland was even required by NIH procedure to have a written agreement in place in order to transfer materials at the time of his collaboration with Pfizer. Does this concern you?

Although it was policy at the NIH to use materials transfer agreements for transfer of all materials outside of the NIH, each IC was allowed to develop policies consistent with their research needs. The new policy that is being developed by our committee on tech transfer will include a requirement for appropriate documentation for transfer of all human samples resulting from human subjects research.

6. Will new NIH policies regarding tracking of human tissues, related data, and human subject protection specify minimum and maximum violations for accidental of willful violations?

We do not anticipate setting specific penalties in advance of the violation, since each circumstance is different. But, NIH will follow the required procedures and discipline employees consistent with the NIH Table of Penalties with respect to punishing individuals who violate rules and regulations.

7. Given what you know now about the correlation between the shipment of human tissue samples and the consulting payments, would you say that Dr. Sunderland not only violated conflict of interest policies, but also violated his fiduciary duties to NIH, and to his patients and volunteers subjects?

It is my understanding that various reviews regarding the matter are underway, and it would be inappropriate for me to venture an opinion about any allegations of misconduct.

RESPONSE FOR THE RECORD OF DAVID L. FRIEDMAN, PH.D.

The Honorable Bart Stupak
Question(s) for David Friedman, Ph. D.
Formerly with Pfizer, Inc.
June 13, 2006
Subcommittee on Oversight and Investigations
Hearing entitled: "Human Tissue Samples: NIH Research Policies and Practices"

1. In his report to an NIMH internal review board, Dr. Sunderland characterized the three-way collaboration involving NIMH, Pfizer, and Oxford Glyocsciences, which yielded no data or publications for NIMH, as unsuccessful. Would you agree with this assessment?

No. I thought it went quite well in a scientific sense.

2. If the collaboration did indeed produce significant findings, why would Dr. Sunderland characterize it as a failure? Would he have any reason to think this was the case?

I noticed that you transitioned from "unsuccessful collaboration" in (1) to a question of failure to produce significant findings in (2). I think the jury is still out on the general utility of these markers as they traverse the validation process. Pfizer continues to update the patent application periodically, perhaps with new and meaningful marker data. That data should be more visible when the patent issues. Perhaps Dr Sunderland felt it was a failure because nothing got published. Perhaps someone should look into that.

3. Did it strike you as odd that Dr. Sunderland did not want to be mentioned in publicity associated with the collaboration involving OGS?

Not really, it wasn't exactly clear why, but not of a scientific concern.

4. Did Dr. Sunderland ever mention why he did not want to be listed? Would there be any reason for a researched interested in publication, and involved in a good-faith collaboration, to not wish to be listed in publicity of this kind?

Not clear to me why.

5. How regularly did Dr. Sunderland visit your lab or OGS while you were in charge of the "unknown biomarkers" research?

First of all, I wasn't "in charge" of the research as you suggest above. I was the scientific leader, albeit with several layers of management above me also on the team (e.g., Michael Silber, Steve Williams). In terms of the regularity of visits, at least quarterly at Pfizer, with perhaps one or two additional visits per year for special "data-driven" events.